Search Strategy

FILE 'USPATFULL' ENTERED AT 16:56:35 ON 20 APRIL 2001

		E	BOYD MICHAEL R/IN
L1	25	S	E3
L2	7	S	CYANOVIRIN?
L3	0	S	L2 NOT L1
L4	7	S	(NOSTOC ELLIPSOSPORUM)
L5	0	S	L4 NOT L1
L6	475	S	CYANOBACTER?
L7	22	S	L6 AND ANTIVIR?
L8	15	S	L7 NOT L1

FILE 'WPIDS' ENTERED AT 17:05:42 ON 20 APRIL 2001

		E	BOYD M R/IN
L9	32	S	E3
L10	5	S	L9 AND CYANOVIR?
L11	5	S	CYANOVIRIN?
L12	5	S	(NOSTOC ELLIPSOSPORUM)
L13	2	S	L12 NOT L10
L14	150	S	CYANOBACTER?
L15	2	S	L14 AND ANTIVIR?

FILE 'MEDLINE' ENTERED AT 17:13:28 ON 20 APRIL 2001

		E	BOYD M R/AU
L16	271	S	E3
L17	13	S	L16 AND CYANOVIRIN?
L18	4	S	L16 AND (NOSTOC ELLIPSOSPORUM)
L19	0	S	L18 NOT L17
L20	8	S	L16 AND CYANOBACT?
L21	2	S	L20 NOT L17
L22	46	S	L16 AND ANTIVIRAL?
L23	41	S	L22 NOT L17
L24	25	S	L23 AND (HIV OR SIV)
L25	16	S	CYANOVIRIN?
L26	3	S	L25 NOT L16

L1 ANSWER 1 OF 25 USPATFULL
2001:29136 Anti-cyanovirin antibody with an internal image of gp120, a method of use thereof, and a method of using a cyanovirin to induce an immune response to gp120.
Boyd, Michael R. , Ijamsville, MD, United States
The United States of America as represented by the Department of Health & Human Services, Washington, DC, United States (U.S. government)
US 6193982 20010227
APPLICATION: US 1998-136594 19980819 (9)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides an anti-cyanovirin antibody with an internal image of gp120, a method of using an anti-cyanovirin antibody with an internal image of gp120 to induce an immune response to gp120 so as to prevent or treat a viral infection in an animal, and a method of using a cyanovirin to induce an immune response to gp120 so as to prevent or treat a viral infection in an animal.

CLM What is claimed is:
1. An anti-cyanovirin antibody, wherein said antibody has an internal image of gp120 of an immunodeficiency virus and can compete with gp120 of an immunodeficiency virus for binding to a cyanovirin, wherein said cyanovirin comprises SEQ ID NO: 2.

2. The anti-cyanovirin antibody of claim 1, wherein said immunodeficiency virus is HIV-1 or HIV-2.

3. A method of inducing an immune response to an immunodeficiency virus in an animal, which method comprises administering to said animal an anti-cyanovirin antibody of claim 2 in an amount sufficient to induce in said animal an immune response to an immunodeficiency virus.

4. A method of inducing an immune response to an immunodeficiency virus in an animal, which method comprises administering to said animal a cyanovirin, wherein said cyanovirin comprises SEQ ID NO: 2 and binds gp120 of an immunodeficiency virus, in all amount sufficient to induce in said animal an anti-cyanovirin antibody, wherein said amount is sufficient to induce an immune response to an immunodeficiency virus.

5. The method of claim 4, wherein said anti-cyanovirin antibody can compete with gp120 of an imrmunodeficiency virus for binding to a cyanovirin.

6. The method of claim 4, wherein said immunodeficiency virus is HIV-1 or HIV-2.

7. A method of selecting an anti-cyanovirin antibody that has an internal image of gp120 of an immunodeficiency virus, which method comprises: (a) contacting a sample of anti-cyanovirin antibodies with gp120 and cyanovirin, wherein said cyanovirin comprises SEQ ID NO:2, and (b) selecting an anti-cyanovirin antibody that competes with gp120 for binding to cyanovirin, whereupon an anti-cyanovirin antibody that has an internal image of gp120 of an immunodeficiency virus is selected.

8. The method of claim 7, wherein said immunodeficiency virus is HIV-1 or HIV-2.

9. A method of selecting an anti-cyanovirin antibody that has an internal image of gp120 of an immunodeficiency virus, which method

comprises: (a) contacting a sample of anti-cyanovirin antibodies with cyanovirin and cyanovirin to which is bound gp120; and (b) selecting an anti-cyanovirin antibody that binds to cyanovirin as opposed to cyanovirin to which is bound gp120, whereupon an anti-cyanovirin antibody that has an internal image of gp120 of an immunodeficiency virus is selected.

10. The method of claim 9, wherein said immunodeficiency virus is HIV-1 or HIV-2.

L1 ANSWER 3 OF 25 USPATFULL
2000:7377 Method of using cyanovirins.
Boyd, Michael R. , Ijamsville, MD, United States
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. corporation)
US 6015876 20000118
APPLICATION: US 1997-969378 19971113 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides antiviral proteins, peptides and conjugates as well as methods of obtaining these agents. The antiviral proteins, peptides and conjugates of the present invention can be used alone or in combination with other antiviral agents in compositions, such as pharmaceutical compositions, to inhibit the infectivity, replication and cytopathic effects of a virus, such as a retrovirus, in particular a human immunodeficiency virus, specifically HIV-1 or HIV-2, in the treatment or prevention of viral infection.

CLM What is claimed is:
1. A method of treating an inanimate object with an antiviral agent, which method comprises contacting said inanimate object with an antiviral effective amount of an isolated and purified antiviral agent selected from the group consisting of an antiviral protein, an antiviral peptide, an antiviral protein conjugate, and an antiviral peptide conjugate, wherein said protein or peptide is encoded by an isolated and purified nucleic acid molecule encoding at least nine contiguous amino acids of SEQ ID NO:2, wherein said at least nine contiguous amino acids of SEQ ID NO:2 has antiviral activity.

2. The method of claim 1, wherein said inanimate object is selected from the group consisting of medical equipment, medical supplies, laboratory equipment and laboratory supplies.

3. The method of claim 2, wherein said inanimate object is a medical tubing.

4. A method of treating ex vivo a bodily product or tissue with an antiviral agent, which method comprises contacting ex vivo said bodily product or tissue with an antiviral effective amount of an isolated and purified antiviral agent selected from the group consisting of an antiviral protein, an antiviral peptide, an antiviral protein conjugate, and an antiviral peptide conjugate, wherein said protein or peptide is encoded by an isolated and purified nucleic acid molecule encoding at least nine contiguous amino acids of SEQ ID NO:2, wherein said at least nine contiguous amino acids of SEQ ID NO:2 has antiviral activity.

5. The method of claim 4, wherein said bodily product is blood, a product of blood, or sperm.

6. The method of claim 4, wherein said antiviral protein, antiviral

peptide, antiviral protein conjugate or antiviral peptide conjugate is present on or in medical equipment, medical supplies, laboratory equipment, laboratory supplies or any solution, suspension, emulsion or other material.

7. The method of claim 6, wherein said antiviral protein, antiviral peptide, antiviral protein conjugate or antiviral peptide conjugate is present on the wall of a medical tubing.

8. The method of claim 4, wherein said antiviral protein, antiviral peptide, antiviral protein conjugate or antiviral peptide conjugate is attached to or part of a solid support matrix.

9. The method of claim 8, wherein said protein or peptide binds to gp120 of HIV.

10. A method of treating any solution, suspension, emulsion or other material with an antiviral agent, which method comprises contacting said solution, suspension, emulsion or other material with an antiviral effective amount of an isolated and purified antiviral agent selected from the group consisting of an antiviral protein, an antiviral peptide, an antiviral protein conjugate, and an antiviral peptide conjugate, wherein said protein or peptide is encoded by an isolated and purified nucleic acid molecule encoding at least nine contiguous amino acids of SEQ ID NO:2, wherein said at least nine contiguous amino acids of SEQ ID NO:2 has antiviral activity.

11. The method of claim 10, wherein said antiviral protein, antiviral peptide, antiviral protein conjugate or antiviral peptide conjugate is attached to or part of a solid support matrix.

12. The method of claim 11, wherein said protein or peptide binds to gp120 of HIV.

13. A method of contacting a virus with an antiviral agent, which method comprises contacting said virus with an antiviral effective amount of an isolated and purified antiviral agent selected from the group consisting of an antiviral protein, an antiviral peptide, an antiviral protein conjugate, and an antiviral peptide conjugate, wherein said protein or peptide is encoded by an isolated and purified nucleic acid molecule encoding at least nine contiguous amino acids of SEQ ID NO:2, wherein said at least nine contiguous amino acids of SEQ ID NO:2 has antiviral activity.

14. The method of claim 13, wherein said isolated and purified antiviral protein comprises the amino acid sequence of SEQ ID NO:2.

15. The method of claim 13, wherein said virus is a retrovirus.

16. The method of claim 15, wherein said retrovirus is a human immunodeficiency virus.

17. The method of claim 16, wherein said human immunodeficiency virus is HIV-1 or HIV-2.

18. The method of claim 13, wherein said antiviral protein, antiviral peptide, antiviral protein conjugate or antiviral peptide conjugate is attached to or part of a solid support matrix.

19. The method of claim 18, wherein said protein or peptide binds to gp120 of HIV.

L1 ANSWER 4 OF 25 USPATFULL
1999:160203 Anti-cyanovirin antibody.
Boyd, Michael R. , Ijamsville, MD, United States
Gustafson, Kirk R., Frederick, MD, United States
Shoemaker, Robert H., Frederick, MD, United States
McMahon, James B., Frederick, MD, United States
The United States of America, represented by the Secretary of the Department of Health and Human Services, Washington, DC, United States (U.S. corporation)
US 5998587 19991207
APPLICATION: US 1997-969249 19971113 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides antiviral proteins (collectively referred to as cyanovirins), conjugates thereof, DNA sequences ending such agents, host cells containing such DNA sequences, antibodies directed to such agents, compositions comprising such agents, and methods of obtaining and using such agents.

CLM What is claimed is:
1. An anti-cyanovirin antibody, wherein said antibody binds an epitope of an antiviral protein isolated and purified from Nostoc ellipsosporum or an epitope of an antiviral peptide isolated and purified from Nostoc ellipsosporum, wherein said antiviral protein and said antiviral peptide comprise at least nine contiguous amino acids of SEQ ID NO:2.

2. The anti-cyanovirin antibody of claim 1, wherein said antiviral protein comprises SEQ ID NO:2.

L1 ANSWER 5 OF 25 USPATFULL
1999:121569 Nucleic acids encoding antiviral proteins and peptides fused to effector proteins.
Boyd, Michael R. , Ijamsville, MD, United States
Shoemaker, Robert H., Frederick, MD, United States
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 5962668 19991005
APPLICATION: US 1997-970179 19971113 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides antiviral proteins (collectively referred to as cyanovirins), conjugates thereof, DNA sequences encoding such agents, host cells containing such DNA sequences, antibodies directed to such agents, compositions comprising such agents, and methods of obtaining and using such agents.

CLM What is claimed is:
1. An isolated and purified nucleic acid molecule comprising a first nucleic acid sequence selected from the group consisting of a nucleic acid sequence encoding at least nine contiguous amino acids of SEQ ID NO:2, a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:4, a nucleic acid sequence comprising the sequence of SEQ ID NO:1, a nucleic acid sequence comprising the sequence of SEQ ID NO:3 coupled to a second nucleic acid sequence encoding an effector protein, wherein said first nucleic acid sequence encodes a peptide or protein having antiviral activity.

2. The nucleic acid molecule of claim 1, wherein said effector protein

is selected from the group consisting of a toxin and an immunological reagent.

3. The nucleic acid molecule of claim 2, wherein said effector protein is a Pseudomonas exotoxin.

4. An isolated and purified nucleic acid molecule comprising a first nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:2 coupled to a second nucleic acid sequence encoding an effector protein.

L1 ANSWER 6 OF 25 USPATFULL
1999:121554 Methods of obtaining antiviral proteins and antiviral peptides from Nostoc ellipsosporum.
Boyd, Michael R. , Ijamsville, MD, United States
Gustafson, Kirk R., Frederick, MD, United States
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 5962653 19991005
APPLICATION: US 1997-969584 19971113 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides antiviral proteins, peptides and conjugates, as well as methods of obtaining these agents. The antiviral proteins, peptides and conjugates of the present invention can be used alone or in combination with other antiviral agents in compositions, such as pharmaceutical compositions, to inhibit the infectivity, replication and cytopathic effects of a virus, such as a retrovirus, in particular a human immunodeficiency virus, specifically HIV-1 or HIV-2, in the treatment or prevention of viral infection.

CLM What is claimed is:
1. A method of obtaining an antiviral protein or antiviral peptide from Nostoc ellipsosporum, which method comprises: (a) identifying an extract of Nostoc ellipsosporum containing antiviral activity, (b) optionally removing high molecular weight biopolymers from said extract, (c) antiviral bioassay-guided fractionating said extract to obtain a crude extract of said protein or peptide, and (d) purifying said crude extract by reverse-phase HPLC to obtain said protein or peptide.

2. The method of claim 1, wherein said antiviral protein or antiviral peptide comprises at least nine contiguous amino acids of SEQ ID NO:2.

3. The method of claim 1, wherein said antiviral protein or antiviral peptide comprises the amino acid sequence of SEQ ID NO:2 or a fragment thereof, wherein said fragment has antiviral activity.

L1 ANSWER 9 OF 25 USPATFULL
1998:150886 Antiviral proteins and peptides.
Boyd, Michael R. , Ijamsville, MD, United States
Gustafson, Kirk R., Frederick, MD, United States
Shoemaker, Robert H., No. Potomac, MD, United States
McMahon, James B., Frederick, MD, United States
The United States of America as Represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 5843882 19981201
APPLICATION: US 1995-429965 19950427 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides antiviral proteins, peptides and

conjugates, as well as methods of obtaining these agents. The antiviral proteins, peptides and conjugates of the present invention can be used alone or in combination with other antiviral agents in compositions, such as pharmaceutical compositions, to inhibit the infectivity, replication and cytopathic effects of a virus, such as a retrovirus, in particular a human immunodeficiency virus, specifically HIV-1 or HIV-2, in the treatment or prevention of viral infection.

CLM What is claimed is:

1. An isolated and purified antiviral protein or antiviral peptide from Nostoc ellipsosporum, wherein said protein or peptide comprises at least nine contiguous amino acids of SEQ ID NO: 2.

2. An isolated and purified antiviral protein or antiviral peptide, wherein said protein or peptide is encoded by an isolated and purified nucleic acid molecule encoding at least nine contiguous amino acids of SEQ ID NO: 2, wherein said at least nine contiguous amino acids of SEQ ID NO: 2 has antiviral activity.

3. A conjugate comprising the protein or peptide of claim 2 coupled to an effector molecule.

4. The conjugate of claim 3, wherein said effector molecule targets HIV glycoprotein gp120.

5. The protein conjugate of claim 4, wherein said effector molecule is selected from the group consisting of a toxin and an immunological reagent.

6. A composition comprising an antiviral effective amount of the protein or peptide of claim 2 and a carrier therefor.

7. An isolated and purified antiviral protein comprising the amino acid sequence of SEQ ID NO: 2 or a fragment thereof, wherein said fragment has antiviral activity.

8. The isolated and purified antiviral protein of claim 7, wherein said protein comprises the amino acid sequence of SEQ ID NO: 2.

9. A conjugate comprising the protein of claim 8 coupled to an effector molecule.

10. A composition comprising an antiviral effective amount of the protein or peptide of claim 8 and a carrier therefor.

11. A conjugate comprising the protein of claim 7 coupled to an effector molecule.

12. The conjugate of claim 11, wherein said conjugate binds HIV glycoprotein gp120.

13. The conjugate of claim 12, wherein said effector molecule is selected from the group consisting of a toxin and an immunological reagent.

14. The protein conjugate of claim 13, wherein said effector molecule is a Pseudomonas exotoxin.

15. A composition comprising an antiviral effective amount of the protein of claim 7 and a carrier therefor.

16. An isolated and purified antiviral peptide comprising a fragment of the amino acid sequence of SEQ ID NO: 2, wherein said fragment has antiviral activity.

17. A conjugate comprising the peptide of claim 16 coupled to an effector molecule.

18. The conjugate of claim 17, wherein said conjugate binds HIV glycoprotein gp120.

19. The conjugate of claim 18, wherein said effector molecule is selected from the group consisting of a toxin and an immunological reagent.

20. The conjugate of claim 19, wherein said effector molecule is a Pseudomonas exotoxin.

21. A composition comprising an antiviral effective amount of the peptide of claim 16 and a carrier therefor.

L1 ANSWER 10 OF 25 USPATFULL
1998:124412 Nucleic acids encoding antiviral proteins and peptides, vectors and host cells comprising same, and methods of producing the antiviral proteins and peptides.
Boyd, Michael R. , Ijamsville, MD, United States
Gustafson, Kirk R., Frederick, MD, United States
Shoemaker, Robert H., Frederick, MD, United States
McMahon, James B., Frederick, MD, United States
The United States of Americaa as represented by the Secretary of the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 5821081 19981013
APPLICATION: US 1996-638610 19960426 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides antiviral proteins (collectively referred to as cyanovirins), conjugates thereof, DNA sequences encoding such agents, host cells containing such DNA sequences, antibodies directed to such agents, compositions comprising such agents, and methods of obtaining and using such agents.

CLM What is claimed is:
1. An isolated and purified nucleic acid molecule selected from the group consisting of (a) a nucleic acid molecule that encodes at least nine contiguous amino acids of SEQ ID NO: 2, (b) a nucleic acid molecule that encodes the amino acid sequence of SEQ ID NO: 4, (c) a nucleic acid molecule that comprises the sequence of SEQ ID NO: 1, (d) a nucleic acid molecule that comprises the sequence of SEQ ID NO: 3, and (e) a nucleic acid molecule that comprises a nucleic acid sequence, which encodes at least nine contiguous amino acids of SEQ ID NO: 2 wherein said isolated and purified nucleic acid molecule encodes a peptide or protein having antiviral activity.

2. The isolated and purified nucleic acid molecule of claim 1 , which encodes the amino acid sequence of SEQ ID NO:2.

3. A vector which comprises the nucleic acid molecule of claim 1.

4. A vector which comprises the nucleic acid molecule of claim 2.

5. A host cell containing the vector of claim 3.

6. A host cell containing the vector of claim 4.

7. A method of producing a protein, which method comprises expressing a protein in a host cell of claim 5.

8. A method of producing a protein, which method comprises expressing a protein in a host cell of claim 6.

9. The host cell of claim 5, wherein said host cell is an autologous or a homologous mammalian cell.

10. The host cell of claim 9, wherein said host cell is a nonpathogenic bacterium or a nonpathogenic yeast.

11. The host cell of claim 10, wherein said host cell is a lactobacillus.

12. The host cell of claim 6, wherein said host cell is an autologous or a homologous mammalian cell.

13. The host cell of claim 12, wherein said host cell is a nonpathogenic bacterium or a nonpathogenic yeast.

14. The host cell of claim 13, wherein said host cell is a lactobacillus.

L10 ANSWER 5 OF 5 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1998-567657 [48] WPIDS
CR 1996-497638 [49]; 1999-044625 [04]; 1999-579629 [48]; 2000-052559 [04]
DNC C1998-170557
TI DNA encoding ***cyanovirin*** polypeptide(s) - useful for producing recombinant polypeptides with antiviral activity.
DC B04 D16
IN ***BOYD, M R*** ; GUSTAFSON, K R; MCMAHON, J B; SHOEMAKER, R H
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 1
PI US 5821081 A 19981013 (199848)* 36p
ADT US 5821081 A CIP of US 1995-429965 19950427, US 1996-638610 19960426
PRAI US 1996-638610 19960426; US 1995-429965 19950427

AB US 5821081 A UPAB: 20000124
A nucleic acid molecule that (a) encodes at least 9 contiguous amino acid residues of SEQ ID NO:2 (a sequence of 101 amino acids as defined in the specification), (b) encodes the amino acid sequence of SEQ ID NO:4 (a sequence of 109 amino acids as defined in the specification), (c) comprises the sequence of SEQ ID NO:1 (a genomic DNA sequence of 327 bp as defined in the specification), (d) comprises the sequence of SEQ ID NO:3 (a genomic DNA sequence of 327 bp as defined in the specification) or (e) comprises a nucleic acid sequence which encodes at least 9 contiguous amino acids of SEQ ID NO:2. Also claimed are: (i) a vector containing the nucleic acid molecule, (ii) a host cell containing the vector, and (iii) production of a protein comprising expressing the protein in a host cell.
USE - The sequences are used to produce the corresponding recombinant polypeptides, which are referred to as ***cyanovirins*** , which are derived from the cyanobacterium Nostoc ellipsosporum, and have antiviral activity, e.g. with EC50 values of 0.4-7.6 nM against various HIV-1

L10 ANSWER 4 OF 5 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-579629 [49] WPIDS
CR 1996-497638 [49]; 1998-567657 [48]; 1999-044625 [04]; 2000-052559 [04]
DNC C1999-168602
TI Nucleic acids encoding anti-viral ***cyanovirin*** proteins isolated from cyanobacteria such as Nostoc ellipsosporum useful for treating viral infections (especially human immune deficiency virus).
DC B04 D16
IN ***BOYD, M R*** ; SHOEMAKER, R H
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 1
PI US 5962668 A 19991005 (199949)* 33p
ADT US 5962668 A CIP of US 1995-429965 19950427, Div ex US 1996-638610 19960426, US 1997-970179 19971113
FDT US 5962668 A Div ex US 5821081, CIP of US 5843882
PRAI US 1996-638610 19960426; US 1995-429965 19950427; US 1997-970179 19971113

AB US 5962668 A UPAB: 20000124
NOVELTY - Nucleic acids (I) encoding anti-viral proteins (homologous to ***cyanovirins*** isolated from cyanobacteria such as Nostoc ellipsosporum) coupled to effector proteins, are new.
DETAILED DESCRIPTION - Isolated and purified nucleic acid molecules (I) encoding anti-viral proteins (homologous to ***cyanovirins*** isolated from cyanobacteria such as Nostoc ellipsosporum) coupled to effector proteins, are new. (I) comprise nucleic acid sequences encoding either 9 or more contiguous amino acids from the amino acid sequence (Ia), amino acid sequence (Ib), amino acid sequence (Ic) or amino acid sequence (Id) coupled to an effector protein (Iep). (Ia) to (Id) have anti-viral

activities and comprise defined 101, 109, 327 and 327 (respectively) amino acid sequences given in the specification.

ACTIVITY - Anti-viral; anti-HIV.

MECHANISM OF ACTION - The ***cyanovirins*** disrupt interaction between the gp20 viral envelope glycoproteins and the CD4+ cell surface receptors. This prevents initial virus-to-cell binding and blocks cell to cell fusion (another route by which the virus is spread).

USE - The nucleic acids may be used in the recombinant production of anti-viral proteins according to standard methodologies. The proteins may then be used to prevent and treat viral infections such as human T lymphotrophic virus (HTLV)-1, HTLV-2, FLV (not defined), SIV (not defined), MLV (not defined), BLV (not defined) and BIV (not defined). They are particularly useful for treating human immune deficiency virus (HIV)-1 (also called HTLV-3) infections.

ADVANTAGE - The proteins encoded by (I):
(i) are effective anti-viral agents;
(ii) act early in the viral life cycle;
(iii) are highly virus specific;
(iv) render the intact virus noninfectious;
(v) prevent the death of the mammalian host cells;
(vi) prevent further viral production;
(vii) prevent the spread of the virus;
(viii) are potent and active against a wide range of strains and isolates of HIV;
(ix) are easy and cheap to produce; and

L10 ANSWER 3 OF 5 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-052559 [04] WPIDS
CR 1996-497638 [49]; 1998-567657 [48]; 1999-044625 [04]; 1999-579629 [48]
DNC C2000-013490
TI An anti- ***cyanovirin*** antibody for use against human immunodeficiency virus.
DC B04 D16
IN ***BOYD, M R*** ; GUSTAFSON, K R; MCMAHON, J B; SHOEMAKER, R H
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 1
PI US 5998587 A 19991207 (200004)* 36p
ADT US 5998587 A CIP of US 1995-429965 19950427, Div ex US 1996-638610 19960426, US 1997-969249 19971113
FDT US 5998587 A Div ex US 5821081, CIP of US 5843882
PRAI US 1996-638610 19960426; US 1995-429965 19950427; US 1997-969249 19971113

AB US 5998587 A UPAB: 20000124
NOVELTY - An anti- ***cyanovirin*** antibody capable of binding an antiviral protein, or an epitope of an antiviral peptide, isolated and purified from Nostoc ellipsosporum is new.

DETAILED DESCRIPTION - The antiviral protein comprises at least nine contiguous amino acids, preferably a 101 amino acid residue sequence given in the specification.

ACTIVITY - Antiviral; anti-HIV.

MECHANISM OF ACTION - None given.

USE - The protein is useful as antiviral agents particularly against

L10 ANSWER 2 OF 5 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-256368 [22] WPIDS
DNN N2000-190630 DNC C2000-078169
TI Anti- ***cyanovirin*** antibody recognizing gp120 of an immunodeficiency virus.
DC B04 D16 S03
IN ***BOYD, M R***

PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 86
PI WO 2000011036 A1 20000302 (200022)* EN 80p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9956814 A 20000314 (200031)
US 6193982 B1 20010227 (200114)
ADT WO 2000011036 A1 WO 1999-US18975 19990819; AU 9956814 A AU 1999-56814 19990819; US 6193982 B1 CIP of US 1995-429965 19950427, Div ex US 1996-638610 19960426, CIP of US 1997-969249 19971113, US 1998-136594 19980819
FDT AU 9956814 A Based on WO 200011036; US 6193982 B1 Div ex US 5821081, CIP of US 5843882, CIP of US 5998587
PRAI US 1998-136594 19980819; US 1995-429965 19950427; US 1996-638610 19960426; US 1997-969249 19971113

AB WO 200011036 A UPAB: 20000508
NOVELTY - An anti- ***cyanovirin*** antibody (Ab), is new, and has an internal image of gp120 of an immunodeficiency virus.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a method of inhibiting a viral infection in an animal, the method comprises administering to the animal an anti- ***cyanovirin*** Ab as above in an amount sufficient to induce in the animal an immune response to a virus sufficient to inhibit an infection of the animal with the virus;

(2) a method of inhibiting a viral infection in an animal, the method comprises administering to the animal a ***cyanovirin*** , which binds gp120 of an immunodeficiency virus, in an amount sufficient to induce an immune response to a virus sufficient to inhibit an infection of the animal with the virus;

(3) a method of selecting an anti- ***cyanovirin*** Ab that has an internal image of gp120 of an immunodeficiency virus, the method comprising:

(a) contacting a sample of anti- ***cyanovirin*** Abs with gp120 and ***cyanovirin*** ; and

(b) selecting anti- ***cyanovirin*** Abs that compete with gp120 for binding to ***cyanovirin*** ; and

(4) a method of selecting an anti- ***cyanovirin*** Ab that has an internal image of gp120 of an immunodeficiency virus, comprising:

(a) contacting a sample of anti- ***cyanovirin*** Abs with ***cyanovirin*** and ***cyanovirin*** which is bound to gp120; and

(b) selecting anti- ***cyanovirin*** Abs that bind to ***cyanovirin*** as opposed to ***cyanovirin*** which is bound to gp120.

ACTIVITY - Antiviral.

MECHANISM OF ACTION - Vaccine.

USE - The anti- ***cyanovirin*** Ab can be used in a method for inhibiting viral infection, preferably HIV-1 or HIV-2 infection, in an animal (claimed). The antibodies can also be used to treat other retroviruses, including Type C and Type D retroviruses, HTLV-1, HTLV-2, HIV, FLV, SIV, MLV, BLV, BIV, equine infectious virus, anemia virus, avian sarcoma viruses, hepatitis type A, B, non-A and non-B viruses, arboviruses, varicella viruses, measles, mumps and rubella viruses.

L10 ANSWER 1 OF 5 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-618771 [59] WPIDS
DNN N2000-458589 DNC C2000-185282

TI Removing virus from sample involves treating sample with composition comprising solid support matrix attached to ***cyanovirin*** , its conjugate or conjugate comprising a ***cyanovirin*** coupled to anti-***cyanovirin*** antibody.
DC A96 B04 D16 D22 P32 P34
IN ***BOYD, M R***
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 91
PI WO 2000053213 A2 20000914 (200059)* EN 93p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000035231 A 20000928 (200067)
ADT WO 2000053213 A2 WO 2000-US6247 20000310; AU 2000035231 A AU 2000-35231 20000310
FDT AU 2000035231 A Based on WO 200053213
PRAI US 1999-416434 19991012; US 1999-267447 19990312

AB WO 200053213 A UPAB: 20001117
NOVELTY - A method for removing (M1) virus from a sample, is new.

DETAILED DESCRIPTION - A method for removing (M1) virus from a sample involves contacting the sample (S) with a composition (I) comprising an isolated and purified antiviral protein, peptide (both of which comprise 9 contiguous amino acids of a fully defined 101 amino acid sequence (S2) (given in the specification), that bind to the virus) and their conjugates which are attached to a solid support matrix, and then separating (S) and (I).

Optionally the method involves contacting the sample with (I), contacting the sample with a matrix-anchored anti- ***cyanovirin*** antibody which binds the antiviral peptide, antiviral protein, antiviral peptide conjugate or antiviral protein conjugate to which the virus is bound and separating the matrix-anchored anti- ***cyanovirin*** antibody and then separating the matrix-anchored anti- ***cyanovirin*** antibody and the sample such that the virus is removed from the sample.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition (C1) comprising a solid support matrix to which is attached an isolated and purified antiviral protein, antiviral peptide (which comprise nine contiguous amino acid sequence of (S2) that binds to a virus), antiviral protein conjugate or antiviral peptide conjugate;

(2) a conjugate (II) comprising an isolated and purified antiviral protein or antiviral peptide comprising nine contiguous amino acids of (S2), that bind to a virus, coupled to an anti- ***cyanovirin*** antibody or one effector component, which can be the same or different groups such as polyethylene glycol, dextran or albumin;

(3) a composition comprising (II);

(4) a method (M2) of inhibiting prophylactically or therapeutically, a viral infection of a host, which comprises topically administering to a host an antiviral agent which is an antiviral peptide, an antiviral protein conjugate or a antiviral peptide conjugate in which antiviral protein or antiviral peptide comprises 9 contiguous amino acids of (S2) which have antiviral activity and the antiviral protein, antiviral peptide or antiviral protein or peptide conjugate is attached to a solid matrix, such that viral infection is inhibited; and

(5) a matrix-anchored anti- ***cyanovirin*** antibody (III), where the antibody binds to an epitope of an antiviral protein or an antiviral peptide comprising nine contiguous amino acids of (S2), where the antibody is attached to a solid-support matrix.

ACTIVITY - Antiviral; anti-HIV. The anti-HIV activity of the

cyanovirin polypeptides were tested in vitro. ***Cyanovirin*** solution were serially diluted in complete medium and added to 96-well test plates. Uninfected CEM-SS cells were plated at a density of 1 x 104 cells in 50 micro l of complete medium. Diluted HIV-1 was then added to the final volume in each microtiter well was 200 micro l. Quadruplicate wells were used for virus-infected cells. Plates were incubated at 37 deg. C in an atmosphere containing 5% CO2 for 4, 5 or 6 days. Subsequently, aliquots of cell-free supernatant were removed from each well and analyzed for reverse transcriptase activity, p24 antigen production and synthesis of infectious virions as described. Cellular growth or viability then was estimated on the remaining contents of each well. The results showed that ***cyanovirin*** -N was capable of complete inhibition of the cytopathic effects of HIV-1 upon CEM-SS human lymphoblastoid target cells in vitro, direct cytotoxicity of the protein upon the target cells was not observed at the highest tested concentrations. ***Cyanovirin*** -N also strikingly inhibited the production of RT, p24, and SFU in HIV-1-infected CEM-SS cells within these same inhibitory effective concentrations, indicating that the protein halted viral replication.

MECHANISM OF ACTION - gp120-mediated binding and fusion of intact HIV-i virions to host cells blocker; inhibitor of cell-to-cell fusion and virus transmission.

USE - (II) and C1 are used for inhibiting prophylactically or therapeutically a viral infection of a host, such that viral infection is

L13 ANSWER 1 OF 2 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-044625 [04] WPIDS
CR 1996-497638 [49]; 1998-567657 [48]; 1999-579629 [48]; 2000-052559 [04]
DNC C1999-013929
TI ***Nostoc*** ***ellipsosporum*** proteins or peptide(s) - with antiviral activity.
DC B04
IN BOYD, M R; GUSTAFSON, K R; MCMAHON, J B; SHOEMAKER, R H
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 1
PI US 5843882 A 19981201 (199904)* 30p
ADT US 5843882 A US 1995-429965 19950427
PRAI US 1995-429965 19950427

AB US 5843882 A UPAB: 20000124
An antiviral protein or peptide from ***Nostoc*** ***ellipsosporum*** is new. The protein or peptide comprises at least 9 contiguous amino acids from a 101 amino acid sequence (I) given in the specification. Also claimed are: (1) an antiviral protein or peptide encoded by a nucleic acid encoding at least 9 contiguous amino acids of (I); (2) a conjugate comprising the protein or peptide of (1) coupled to an effector molecule; (3) an antiviral protein comprising (I) or a fragment of it, where the fragment has antiviral activity; (4) a conjugate comprising the protein of (3) coupled to an effector molecule; (5) an antiviral peptide comprising a fragment of (I), where the fragment has antiviral activity; (6) a conjugate comprising the peptide of (5) coupled to an effector molecule.

USE - The antiviral protein or peptide is used to inhibit the infectivity, replication and cytopathic effects of viruses, especially HIV-1 or HIV-2, in the treatment or prevention of viral infections.

L13 ANSWER 2 OF 2 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1996-497638 [49] WPIDS
CR 1998-567657 [48]; 1999-044625 [04]; 1999-579629 [48]; 2000-052559 [04]
DNC C1996-155620
TI Antiviral protein from ***Nostoc*** ***ellipsosporum*** - used for treating or preventing viral infections, esp. infections caused by retro

viruses such as HIV.
DC B04 D16
IN BOYD, M R; GUSTAFSON, K R; MCMAHON, J B; SHOEMAKER, R H
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 71
PI WO 9634107 A2 19961031 (199649)* EN 99p
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN
AU 9656691 A 19961118 (199710)
WO 9634107 A3 19970424 (199731)
EP 836647 A2 19980422 (199820) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 11504804 W 19990511 (199929) 84p
AU 707781 B 19990722 (199940)
US 5962653 A 19991005 (199948)
US 6015876 A 20000118 (200011)
AU 9956039 A 20000106 (200013)#
ADT WO 9634107 A2 WO 1996-US5908 19960426; AU 9656691 A AU 1996-56691 19960426; EP 836647 A2 EP 1996-913854 19960426, WO 1996-US5908 19960426; JP 11504804 W JP 1996-532778 19960426, WO 1996-US5908 19960426; AU 707781 B AU 1996-56691 19960426; US 5962653 A Div ex US 1995-429965 19950427, US 1997-969584 19971113; US 6015876 A Div ex US 1995-429965 19950427, US 1997-969378 19971113; AU 9956039 A Div ex AU 1996-56691 19960426, AU 1999-56039 19991022
FDT AU 9656691 A Based on WO 9634107; EP 836647 A2 Based on WO 9634107; JP 11504804 W Based on WO 9634107; AU 707781 B Previous Publ. AU 9656691, Based on WO 9634107; AU 9956039 A Div ex AU 707781
PRAI US 1995-429965 19950427; US 1997-969584 19971113; US 1997-969378 19971113; AU 1999-56039 19991022

AB WO 9634107 A UPAB: 20000313
An isolated and purified antiviral protein (A) comprising at least 9 contiguous amino acids of a 101 amino acid residue sequence (given in the specification) is claimed. Also claimed are: (1) a protein conjugate comprising (A) coupled to an effector mol.; (2) an isolated and purified nucleic acid molecule (I) which encodes (A) or the conjugate of (1); (3) a vector which comprises (1); (4) a host cell contg. a vector as in (3); and (5) an antibody which binds (A).

USE - The antiviral protein has high activity against immunodeficiency retroviruses, partic. HIV. It can be used for treating or preventing viral infections in animals (claimed). It can also be used for preventing the spread of viral infections by treating inanimate objects, ex vivo blood, blood prods. or tissue (claimed).

L17 ANSWER 1 OF 13 MEDLINE
2001018270 Document Number: 20495188. PubMed ID: 11040045. Analysis of the interaction between the HIV-inactivating protein ***cyanovirin*** -N and soluble forms of the envelope glycoproteins gp120 and gp41. O'Keefe B R; Shenoy S R; Xie D; Zhang W; Muschik J M; Currens M J; Chaiken I; ***Boyd M R*** . (Laboratory of Drug Discovery Research and Development, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, SAIC Frederick, Frederick Cancer Research and Development Center, Frederick, Maryland, USA.) MOLECULAR PHARMACOLOGY, (2000 Nov) 58 (5) 982-92. Journal code: NGR. ISSN: 0026-895X. Pub. country: United States. Language: English.

AB The novel virucidal protein ***cyanovirin*** -N (CV-N) binds with equally high affinity to soluble forms of either H9 cell-produced or recombinant glycosylated HIV-1 gp120 (sgp120) or gp160 (sgp160). Fluorescence polarization studies showed that CV-N is also capable of binding to the glycosylated ectodomain of the HIV-envelope protein gp41 (sgp41) (as well as SIV glycoprotein 32), albeit with considerably lower affinity than the sgp120/CV-N interaction. Pretreatment of CV-N with either sgp120 or sgp41 abrogated the neutralizing activity of CV-N against intact, infectious HIV-1 virions. Isothermal calorimetry and optical biosensor binding studies showed that CV-N bound to recombinant sgp120 with a K(d) value ranging from 2 to 45 nM and to sgp41 with a K(d) value of 606 nM; furthermore, they indicated an approximate 5:1 stoichiometry for CV-N binding to sgp120 and a 1:1 stoichiometry for CV-N binding to sgp41. Circular dichroism studies additionally illuminated the binding of CV-N with both sgp120 and sgp41, providing the first direct evidence that conformational changes are a consequence of CV-N interactions with both HIV-1 envelope glycoproteins.

L17 ANSWER 2 OF 13 MEDLINE
2000386291 Document Number: 20353708. PubMed ID: 10894760. Development of a ***cyanovirin*** -N-HIV-1 gp120 binding assay for high throughput screening of natural product extracts by time-resolved fluorescence. McMahon J B; Beutler J A; O'Keefe B R; Goodrum C B; Myers M A; ***Boyd M*** *** R*** . (Laboratory of Drug Discovery Research and Development, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD 21702-1201, USA.) J Biomol Screen, (2000 Jun) 5 (3) 169-76. Journal code: DOE; 9612112. ISSN: 1087-0571. Pub. country: United States. Language: English.

AB The unique, high-affinity binding of ***cyanovirin*** -N (CV-N), a potent anti-human immunodeficiency virus (HIV) protein, to the HIV envelope glycoprotein gp120, was exploited to develop an HTS assay in an attempt to discover small-molecule mimetics of CV-N. A competition binding assay was developed using CV-N labeled with europium (Eu(3+)). The labeling protocol did not significantly alter the gp120 binding properties or the antiviral activity of CV-N. This report describes the assay development, validation, and results of screening a large library of aqueous and organic natural product extracts. The extracts were incubated with immobilized recombinant gp120 in 96-well plates prior to the addition of Eu(3+)-labeled CV-N. Following a wash step, bound CV-N was measured by dissociation-enhanced time-resolved fluorometry of Eu(3+). The assay proved to be robust, rapid, and reproducible, and was used to screen over 50,000 natural product extracts, and has resulted in the identification of several aqueous natural product extracts that inhibited CV-N-gp120 binding and also had anti-HIV activity.

L17 ANSWER 3 OF 13 MEDLINE

2000252075 Document Number: 20252075. PubMed ID: 10794101. Properties of ***cyanovirin*** -N (CV-N): inactivation of HIV-1 by sessile ***cyanovirin*** -N (sCV-N). Gandhi M J; ***Boyd M R*** ; Yi L; Yang G G; Vyas G N. (Department of Laboratory Medicine, University of California, San Francisco, USA.) DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, (2000) 102 141-8. Ref: 14. Journal code: E7V; 0427140. ISSN: 0301-5149. Pub. country: Switzerland. Language: English.

AB ***Cyanovirin*** -N (CV-N) is a novel anti-HIV protein isolated and characterized from a cyanobacterium Nostoc ellipsosporum. CV-N protein is a single 101 amino acid chain containing two intrachain disulphide bonds and considerable internal sequence duplication, but no significant homology to previously described proteins or to the transcription products of known nucleotide sequences. In solution, CV-N exists largely as a beta-sheet protein with internal two-fold pseudosymmetry. CV-N irreversibly inactivates diverse laboratory strains, primary isolates and clades of HIV-1, as well as strains of HIV-2 and simian immunodeficiency virus (SIV). CV-N binds with extremely high affinity to highly conserved binding site(s) on the viral envelope glycoprotein gp120, preventing virus-to-cell fusion, viral entry and infection of cells. The CV-N binding site appears to overlap, but is not identical with, the unique carbohydrate-dependent epitope 2G12, and may lie predominantly within an immunologically "silent" region of gp120. CV-N is undergoing preclinical development for topical anti-HIV prophylactic (e.g., microbicidal) applications to prevent sexual transmission of HIV. Since CV-N may be immunogenic in humans, methods for using CV-N for ex vivo inactivation of HIV in blood, plasma, or putative vaccines preferably would allow for its exclusion from biologicals for parenteral use. To explore this concept we biotinylated CV-N (bCV-N) and coupled it to streptavidin coated magnetic beads to provide a product which we termed sessile CV-N (sCV-N). When reacted with a laboratory strain and a primary isolate of HIV- 1, the sCV-N completely inactivated 100 TCID50 of the virus. However RT-PCR of the viral extracts indicated that only a fraction of the virus was removed by the sCV-N, leaving behind a relatively larger fraction of non-infectious virus in the supernatant which we designated as replication incompetent virions (RIV). It would be worthwhile investigating the role of RIV as a putative HIV vaccine.

L17 ANSWER 4 OF 13 MEDLINE

2000240039 Document Number: 20240039. PubMed ID: 10775592. Multiple antiviral activities of ***cyanovirin*** -N: blocking of human immunodeficiency virus type 1 gp120 interaction with CD4 and coreceptor and inhibition of diverse enveloped viruses. Dey B; Lerner D L; Lusso P; ***Boyd M R*** ; Elder J H; Berger E A. (Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892-0445, USA.) JOURNAL OF VIROLOGY, (2000 May) 74 (10) 4562-9. Journal code: KCV; 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB ***Cyanovirin*** -N (CV-N) is a cyanobacterial protein with potent neutralizing activity against human immunodeficiency virus (HIV). CV-N has been shown to bind HIV type 1 (HIV-1) gp120 with high affinity; moreover, it blocks the envelope glycoprotein-mediated membrane fusion reaction associated with HIV-1 entry. However, the inhibitory mechanism(s) remains unclear. In this study, we show that CV-N blocked binding of gp120 to cell-associated CD4. Consistent with this, pretreatment of gp120 with CV-N inhibited soluble CD4 (sCD4)-dependent binding of gp120 to cell-associated CCR5. To investigate possible effects of CV-N at post-CD4 binding steps, we used an assay that measures sCD4 activation of the HIV-1 envelope glycoprotein for fusion with CCR5-expressing cells. CV-N displayed equivalently potent inhibitory effects when added before or after sCD4

activation, suggesting that CV-N also has blocking action at the level of gp120 interaction with coreceptor. This effect was shown not to be due to CV-N-induced coreceptor down-modulation after the CD4 binding step. The multiple activities against the HIV-1 envelope glycoprotein prompted us to examine other enveloped viruses. CV-N potently blocked infection by feline immunodeficiency virus, which utilizes the chemokine receptor CXCR4 as an entry receptor but is CD4 independent. CV-N also inhibited fusion and/or infection by human herpesvirus 6 and measles virus but not by vaccinia virus. Thus, CV-N has broad-spectrum antiviral activity, both for multiple steps in the HIV entry mechanism and for diverse enveloped viruses. This broad specificity has implications for potential clinical utility of CV-N.

L17 ANSWER 5 OF 13 MEDLINE
1999262850 Document Number: 99262850. PubMed ID: 10329150. Crystal structure of ***cyanovirin*** -N, a potent HIV-inactivating protein, shows unexpected domain swapping. Yang F; Bewley C A; Louis J M; Gustafson K R; ***Boyd M R*** ; Gronenborn A M; Clore G M; Wlodawer A. (Macromolecular Structure Laboratory, ABL-Basic Research Program, NCI-Frederick Cancer Research and Development Center, Frederick, MD, 21702-1201, USA.) JOURNAL OF MOLECULAR BIOLOGY, (1999 May 7) 288 (3) 403-12. Journal code: J6V; 2985088R. ISSN: 0022-2836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The crystal structure of ***cyanovirin*** -N (CV-N), a protein with potent antiviral activity, was solved at 1.5 A resolution by molecular replacement using as the search model the solution structure previously determined by NMR. The crystals belong to the space group P3221 with one monomer of CV-N in each asymmetric unit. The primary structure of CV-N contains 101 residues organized in two domains, A (residues 1 to 50) and B (residues 51 to 101), with a high degree of internal sequence and structural similarity. We found that under the conditions of the crystallographic experiments (low pH and 26 % isopropanol), two symmetrically related monomers form a dimer by domain swapping, such that domain A of one monomer interacts with domain B' of its crystallographic symmetry mate and vice versa. Because the two swapped domains are distant from each other, domain swapping does not result in additional intramolecular interactions. Even though one of the protein sample solutions that was used for crystallization clearly contained 100 % monomeric CV-N molecules, as judged by various methods, we were only able to obtain crystals containing domain-swapped dimers. With the exception of the unexpected phenomenon of domain swapping, the crystal structure of CV-N is very similar to the NMR structure, with a root-mean-square deviation of 0.55 A for the main-chain atoms, the best agreement reported to date for structures solved using both techniques.

L17 ANSWER 6 OF 13 MEDLINE
1999214377 Document Number: 99214377. PubMed ID: 10196334.
Cyanovirin -N binds to gp120 to interfere with CD4-dependent human immunodeficiency virus type 1 virion binding, fusion, and infectivity but does not affect the CD4 binding site on gp120 or soluble CD4-induced conformational changes in gp120. Esser M T; Mori T; Mondor I; Sattentau Q J; Dey B; Berger E A; ***Boyd M R*** ; Lifson J D. (Retroviral Pathogenesis Laboratory, AIDS Vaccine Program, SAIC-Frederick, Frederick, Maryland 21702, USA.) JOURNAL OF VIROLOGY, (1999 May) 73 (5) 4360-71. Journal code: KCV; 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB ***Cyanovirin*** -N (CV-N), an 11-kDa protein isolated from the cyanobacterium Nostoc ellipsosporum, potently inactivates diverse strains of human immunodeficiency virus type 1 (HIV-1), HIV-2, and simian

immunodeficiency virus. While it has been well established that the viral surface envelope glycoprotein gp120 is a molecular target of CV-N, the detailed mechanism of action is of further interest. We compared matched native and CV-N-treated virus preparations in a panel of assays that measure viral replication, assessing successive stages of the viral life cycle. CV-N-treated virions failed to infect cells as detected by p24 production and quantitative PCR for HIV-1 reverse transcription products, whereas treatment of the target cells did not block infection, confirming that CV-N acts at the level of the virus, not the target cell, to abort the initial infection process. Compared to native HIV-1 preparations, CV-N-treated HIV-1 virions showed impaired CD4-dependent binding to CD4(+) T cells and did not mediate "fusion from without" of CD4(+) target cells. CV-N also blocked HIV envelope glycoprotein Env-induced, CD4-dependent cell-cell fusion. Mapping studies with monoclonal antibodies (MAbs) to defined epitopes on the HIV-1 envelope glycoprotein indicated that CV-N binds to gp120 in a manner that does not occlude or alter the CD4 binding site or V3 loop or other domains on gp120 recognized by defined MAbs and does not interfere with soluble CD4-induced conformational changes in gp120. Binding of CV-N to soluble gp120 or virions inhibited subsequent binding of the unique neutralizing MAb 2G12, which recognizes a glycosylation-dependent epitope. However, prior binding of 2G12 MAb to gp120 did not block subsequent binding by CV-N. These results help clarify the mechanism of action of CV-N and suggest that the compound may act in part by preventing essential interactions between the envelope glycoprotein and target cell receptors. This proposed mechanism is consistent with the extensive activity profile of CV-N against numerous isolates of HIV-1 and other lentiviruses and supports the potential broad utility of this protein as a microbicide to prevent the sexual transmission of HIV.

L17 ANSWER 7 OF 13 MEDLINE
1998369638 Document Number: 98369638. PubMed ID: 9704015. The HIV-inactivating protein, ***cyanovirin*** -N, does not block gp120-mediated virus-to-cell binding. Mariner J M; McMahon J B; O'Keefe B R; Nagashima K; ***Boyd M R*** . (Laboratory of Drug Discovery Research and Development, National Cancer Institute, Frederick Cancer Research & Development Center, Maryland 21702-1201, USA.) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 Jul 30) 248 (3) 841-5. Journal code: 9Y8; 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Concentrations of the potent, HIV(human immunodeficiency virus) inactivating protein, ***cyanovirin*** -N (CV-N), which completely inhibit HIV-1 infectivity, do not block the binding of soluble CD4-receptor (sCD4) to HIV-1 lysates nor the attachment of intact HIV-1 virions to several target T-cell lines. Furthermore, in contrast to the known disassociative effects of sCD4 on viral envelope glycoproteins, treatment of HIVRF with high concentrations of CV-N results in complete viral inactivation but without apparent shedding of gp120 or other ultrastructural changes. These results are consistent with the view that the virucidal effects of CV-N result from interference with step(s) in the fusion process subsequent to the initial binding of the virus to target cells.

L17 ANSWER 8 OF 13 MEDLINE
1998328108 Document Number: 98328108. PubMed ID: 9665171. Solution structure of ***cyanovirin*** -N, a potent HIV-inactivating protein. Bewley C A; Gustafson K R; ***Boyd M R*** ; Covell D G; Bax A; Clore G M; Gronenborn A M. (Laboratory of Chemical Physics, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892-0520, USA.) NATURE STRUCTURAL BIOLOGY, (1998

Jul) 5 (7) 571-8. Journal code: B98; 9421566. ISSN: 1072-8368. Pub. country: United States. Language: English.

AB The solution structure of ***cyanovirin*** -N, a potent 11,000 Mr HIV-inactivating protein that binds with high affinity and specificity to the HIV surface envelope protein gp120, has been solved by nuclear magnetic resonance spectroscopy, including extensive use of dipolar couplings which provide a priori long range structural information. ***Cyanovirin*** -N is an elongated, largely beta-sheet protein that displays internal two-fold pseudosymmetry. The two sequence repeats (residues 1-50 and 51-101) share 32% sequence identity and superimpose with a backbone atomic root-mean-square difference of 1.3 A. The two repeats, however, do not form separate domains since the overall fold is dependent on numerous contacts between them. Rather, two symmetrically related domains are formed by strand exchange between the two repeats. Analysis of surface hydrophobic clusters suggests the location of potential binding sites for protein-protein interactions.

L17 ANSWER 9 OF 13 MEDLINE
1998191875 Document Number: 98191875. PubMed ID: 9518455. Recombinant production of ***cyanovirin*** -N, a potent human immunodeficiency virus-inactivating protein derived from a cultured cyanobacterium. Mori T; Gustafson K R; Pannell L K; Shoemaker R H; Wu L; McMahon J B; ***Boyd M*** *** R*** . (Laboratory of Drug Discovery Research and Development, Division of Cancer Treatment, Diagnosis and Centers, National Cancer Institute-FCRDC, Frederick, Maryland 21702-1201, USA.) PROTEIN EXPRESSION AND PURIFICATION, (1998 Mar) 12 (2) 151-8. Journal code: BJV; 9101496. ISSN: 1046-5928. Pub. country: United States. Language: English.

AB Here we describe the recombinant production and purification of a novel anti-human immunodeficiency virus (HIV) protein, ***cyanovirin*** -N (CV-N), in Escherichia coli. Initial attempts to express CV-N using a vector containing an ompA signal peptide sequence resulted in production of an intractable mixture of the full-length (101 amino acid residue) protein and a truncated form lacking the first two N-terminal amino acids. The truncated protein was observed regardless of the host cell line, culture conditions, or induction time. These observations suggested that an as yet unidentified protease or peptidase was responsible for proteolytic cleavage between the second and third N-terminal amino acids of CV-N when presented as an ompA-CV-N fusion protein. When the ompA signal peptide sequence was replaced by a pelB signal peptide sequence, CV-N was produced in high yield as a single, homogeneous protein. This was confirmed by electrospray ionization mass spectrometry and N-terminal sequencing. This expression system provides a basis for large-scale production of clinical grade CV-N for further research and development as an anti-HIV microbicide.

L17 ANSWER 10 OF 13 MEDLINE
1998042488 Document Number: 98042488. PubMed ID: 9367864. Construction and enhanced cytotoxicity of a [***cyanovirin*** -N]-[Pseudomonas exotoxin] conjugate against human immunodeficiency virus-infected cells. Mori T; Shoemaker R H; McMahon J B; Gulakowski R J; Gustafson K R; ***Boyd M R*** . (Laboratory of Drug Discovery Research and Development, National Cancer Institute, Frederick, Maryland 21702-1201, USA.) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1997 Oct 29) 239 (3) 884-8. Journal code: 9Y8; 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB ***Cyanovirin*** -N (CV-N) is a novel 11-kDa anti-HIV(human immunodeficiency virus) protein that binds with high affinity to the viral envelope glycoprotein gp120. In contrast to soluble CD4 and most known

neutralizing antibodies that bind gp120, CV-N exerts potent anti-viral activity against primary clinical HIV isolates as well as laboratory-adapted strains of HIV. Here we describe the recombinant production, purification, and characterization of a chimeric toxin molecule, FLAG-CV-N-PE38, that contains CV-N as a gp120-targeting moiety linked to the translocation and cytotoxic domains of Pseudomonas exotoxin A. FLAG-CV-N-PE38 showed enhanced cytotoxicity to HIV-infected, gp120-expressing H9 cells compared to uninfected H9 cells. Competition experiments with free CV-N provided further support that the enhanced FLAG-CV-N-PE38-induced cytotoxicity was due to interactions of the CV-N moiety with cell surface gp120. This study establishes the feasibility of use of CV-N as a gp120-targeting sequence for construction and experimental therapeutic investigations of unique new chimeric toxins designed to selectively destroy HIV-infected host cells.

L17 ANSWER 11 OF 13 MEDLINE
97445156 Document Number: 97445156. PubMed ID: 9299483. Isolation, primary sequence determination, and disulfide bond structure of ***cyanovirin*** -N, an anti-HIV (human immunodeficiency virus) protein from the cyanobacterium Nostoc ellipsosporum. Gustafson K R; Sowder R C 2nd; Henderson L E; Cardellina J H 2nd; McMahon J B; Rajamani U; Pannell L K; ***Boyd M R*** . (Laboratory of Drug Discovery Research and Development, National Cancer Institute, Frederick Cancer Research and Development Center, Maryland 21702-1201, USA.) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1997 Sep 8) 238 (1) 223-8. Journal code: 9Y8; 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB A novel anti-HIV protein, ***cyanovirin*** -N (CV-N), was isolated from an aqueous cellular extract of the cultured cyanobacterium (blue-green alga) Nostoc ellipsosporum, purified by reverse-phase HPLC, and sequenced by N-terminal Edman degradation of the intact protein and peptide fragments produced by endoproteinase digestions. CV-N consists of a single 101 amino acid chain which exhibits significant internal sequence duplication, but no significant homology to previously described proteins or to the transcription products of known nucleotide sequences. Alignment of residues 1-50 with residues 51-101 reveals 13 conservative amino acid changes as well as direct homology between 16 amino acid residues. CV-N contains four cysteines which form two intrachain disulfide bonds. The positions of the disulfide linkages were established by fast atom bombardment mass spectral studies of peptide fragments generated by a tryptic digestion of the native protein. Reductive cleavage of these crosslinks resulted in loss of anti-HIV activity.

L17 ANSWER 12 OF 13 MEDLINE
97445155 Document Number: 97445155. PubMed ID: 9299482. Analysis of sequence requirements for biological activity of ***cyanovirin*** -N, a potent HIV (human immunodeficiency virus)-inactivating protein. Mori T; Shoemaker R H; Gulakowski R J; Krepps B L; McMahon J B; Gustafson K R; Pannell L K; ***Boyd M R*** . (Laboratory of Drug Discovery Research and Development, National Cancer Institute-FCRDC, Frederick, Maryland 21702-1201, USA.) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1997 Sep 8) 238 (1) 218-22. Journal code: 9Y8; 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Site-directed mutagenesis of DNA constructs coding for the novel, HIV-inactivating proteins ***cyanovirin*** -N (CV-N) and FLAG-***cyanovirin*** -N (F-CV-N) was performed using mutagenic oligonucleotide primers in the polymerase chain reaction or by a restriction site elimination maneuver. The mutant constructs were expressed in Escherichia coli and the recombinant protein products were tested for binding to the HIV surface envelope glycoprotein gp 120 and for

antiviral activity against infectious HIV. Results showed an overall very high correlation (r2 > 0.9) between the relative gp120 binding affinities and the anti-HIV activities of CV-N, F-CV-N, and the various mutants. An outlier, however, was a mutant which lacked one of the internal disulfide linkages normally present in CV-N and which showed modest gp120 binding but no antiviral activity against HIV. These findings are consistent with the view that gp120 binding is a necessary but not sufficient requirement for the HIV-inactivating activity of CV-N and related proteins; the sequence specificities for gp120 binding and anti-HIV activity are not identical.

L17 ANSWER 13 OF 13 MEDLINE
97354384 Document Number: 97354384. PubMed ID: 9210678. Discovery of ***cyanovirin*** -N, a novel human immunodeficiency virus-inactivating protein that binds viral surface envelope glycoprotein gp120: potential applications to microbicide development. ***Boyd M R*** ; Gustafson K R; McMahon J B; Shoemaker R H; O'Keefe B R; Mori T; Gulakowski R J; Wu L; Rivera M I; Laurencot C M; Currens M J; Cardellina J H 2nd; Buckheit R W Jr; Nara P L; Pannell L K; Sowder R C 2nd; Henderson L E. (Division of Cancer Treatment, Diagnosis and Centers, National Cancer Institute, Frederick, Maryland 21702-1201, USA.. boyd@dtpax2.ncifcrf.gov) . ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1997 Jul) 41 (7) 1521-30. Journal code: 6HK; 0315061. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB We have isolated and sequenced a novel 11-kDa virucidal protein, named ***cyanovirin*** -N (CV-N), from cultures of the cyanobacterium (blue-green alga) Nostoc ellipsosporum. We also have produced CV-N recombinantly by expression of a corresponding DNA sequence in Escherichia coli. Low nanomolar concentrations of either natural or recombinant CV-N irreversibly inactivate diverse laboratory strains and primary isolates of human immunodeficiency virus (HIV) type 1 as well as strains of HIV type 2 and simian immunodeficiency virus. In addition, CV-N aborts cell-to-cell fusion and transmission of HIV-1 infection. Continuous, 2-day exposures of uninfected CEM-SS cells or peripheral blood lymphocytes to high concentrations (e.g., 9,000 nM) of CV-N were not lethal to these representative host cell types. The antiviral activity of CV-N is due, at least in part, to unique, high-affinity interactions of CV-N with the viral surface envelope glycoprotein gp120. The biological activity of CV-N is highly resistant to physicochemical denaturation, further enhancing its potential as an anti-HIV microbicide.

L29 ANSWER 9 OF 11 MEDLINE
94207480 Document Number: 94207480. PubMed ID: 1344652. Therapeutic aspects of retroviral disease. Peto T. (John Radcliffe Hospital, Headington, Oxford, UK.) BAILLIERES CLINICAL NEUROLOGY, (1992 Apr) 1 (1) 239-57. Ref: 88. Journal code: B0Z; 9214291. ISSN: 0961-0421. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Retroviruses of the nervous system cause HTLV-1-associated myelopathy and HIV-associated diseases. The treatment of HTLV-1 disease is essentially conservative; there is no effective drug treatment and therefore patients should be simply supported and reassured. If appropriate, other members of the family should be tested for HTLV-1 disease and counselled. The effects of HIV on the nervous system are much more complex. Therapy must take account of the diverse complications of HIV disease. Patients are probably best managed in specialized clinics which can cope with the different manifestations of the disease. Zidovudine (AZT) is the only effective anti-HIV drug that is licensed. It is indicated in complicated seroconversion disease and for any manifestation of HIV progression including AIDS dementia complex. Management of severe neurological disease depends critically on the ability to diagnose and treat CNS-specific opportunistic infections. Whether zidovudine is indicated for early asymptomatic disease when CD4 counts are below 500 microliters-1 is controversial. The main problems of zidovudine are reversible anaemia which results in about 30% of patients not tolerating long-term use, and the development of drug resistance which may be associated with ***clinical*** ***failure*** of the drug. Other, new and experimental drug treatments are discussed but none of them has as yet shown any convincing evidence of efficacy. Future improvements in treatment appear to depend on the development of effective multiple drug regimens (concurrently or sequentially) which will overcome the challenge of drug resistance.

L34 ANSWER 16 OF 72 MEDLINE
2000251321 Document Number: 20251321. PubMed ID: 10788598. Design of anti- ***HIV*** compounds: from nucleoside to nucleoside 5'-triphosphate analogs. Problems and perspectives. Kukhanova M; Krayevsky A; Prusoff W; Cheng Y C. (Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, 32 Vavilov St, Moscow, 117984.. kukhan@medmail.com) . CURRENT PHARMACEUTICAL DESIGN, (2000 Mar) 6 (5) 585-98. Ref: 80. Journal code: DA0; 9602487. ISSN: 1381-6128. Pub. country: Netherlands. Language: English.

AB To date, ***human*** ***immunodeficiency*** ***virus*** infection remains incurable although a variety of ***antiviral*** agents have been identified and characterized. Even though nucleoside analogs have been the most successful prodrugs, there remains the need to develop new compounds that exhibit a more favorable toxicity profile, less susceptible to cross- ***resistance*** , and greater efficacy. As prodrugs, the nucleoside analogs should be sequentially phosphorylated by cellular kinases to yield triphosphate form before they can inhibit ***HIV*** replication at the reverse transcriptase level. The efficiency of phosphorylation of nucleoside analogs is a key factor in their ***antiviral*** activity and strongly depends on nucleoside structure and cell type. In recent years, several attempts have been made to improve ***therapeutic*** potential of nucleoside analogs by the use of nucleotide prodrugs (pronucleotides), that can avoid the first step of phosphorylation. This ***review*** focuses on problems of intracellular phosphorylation of nucleoside analogs and perspectives of developing of a new class of nucleotide analogs modified at phosphate group as a form for the delivery of nucleotide analogs into the cell.

L34 ANSWER 17 OF 72 MEDLINE
2000242323 Document Number: 20242323. PubMed ID: 10780051.
Antiviral therapy: current options and challenges. Reusser P. (Department of Medicine, University Hospital, Basel.. pierre.reusser@jura.ch) . SCHWEIZERISCHE MEDIZINISCHE WOCHENSCHRIFT. JOURNAL SUISSE DE MEDECINE, (2000 Jan 29) 130 (4) 101-12. Ref: 105. Journal code: UEI; 0404401. ISSN: 0036-7672. Pub. country: Switzerland. Language: English.

AB This article ***reviews*** current options and concepts for drug treatment of viral infections with the exception of ***human*** ***immunodeficiency*** ***virus*** infection. Advances in ***antiviral*** drug development and in rapid diagnostic methods have resulted in efficient management strategies, particularly for infections due to herpes simplex virus, varicella-zoster virus, cytomegalovirus, influenza A and B viruses, and chronic hepatitis B and C. Newer ***antiviral*** agents, such as valaciclovir and famciclovir, have a high oral bioavailability which permits less frequent intake and avoidance of intravenous therapy in many cases. As an alternative to subcutaneous interferon-alpha (IFN-alpha) treatment, oral lamivudine is now approved for therapy of chronic hepatitis B. The addition of oral ribavirin to IFN-alpha treatment has been shown to be superior to IFN-alpha alone for therapy of chronic hepatitis C. By contrast to amantadine, neuraminidase inhibitors such as zanamivir or oseltamivir (GS4104) have activity against both influenza A and B viruses and are well tolerated. First results of controlled trials with these agents are discussed. The emergence of herpes virus ***resistance*** to ***antiviral*** drugs is of concern, and validation of alternative treatment for patients with documented ***resistance*** is required. Future investigations may also help to clarify the ***therapeutic*** role of novel ***antiviral*** drugs and formulations, such as the oral prodrug of cidofovir, valganciclovir, compounds 1263W94 and Bay 38-4766, and pleconaril.

L34 ANSWER 31 OF 72 MEDLINE
1998160733 Document Number: 98160733. PubMed ID: 9499754. Practical issues regarding the use of antiretroviral therapy for ***HIV*** infection. Deeks S G. (University of California, School of Medicine, San Francisco 94110, USA.. sdeeks@sfaids.ucsf.edu) . WESTERN JOURNAL OF MEDICINE, (1998 Feb) 168 (2) 133-9. Ref: 29. Journal code: XN5; 0410504. ISSN: 0093-0415. Pub. country: United States. Language: English.

AB With the recent development of potent new antiretroviral therapies, the management of ***HIV*** infection has become increasingly complex. There are now 12 antiretroviral drugs approved for use in the management of ***HIV*** infection, with several more in the advanced stages of ***clinical*** development. Staying current with this rapidly changing area of medicine is a challenge to ***clinicians*** caring for ***HIV*** -infected patients. This ***review*** provides an overview of ***HIV*** pathogenesis and discusses the basic principles of therapy. These principles, developed recently by the U.S. Department of Health and Human Services, provide a practical framework to rapidly incorporate new developments into ***clinical*** practice. Each of the three classes of antiretroviral therapies is then explained, focusing on the practical management of side effects, drug interactions, and viral ***resistance*** . The ***antiviral*** activity and ***clinical*** efficacy of each ***therapeutic*** class is ***reviewed*** , with an emphasis on applying current results to ***clinical*** decision making. Finally, recently published treatment guidelines are ***reviewed*** .

L34 ANSWER 43 OF 72 MEDLINE
97030930 Document Number: 97030930. PubMed ID: 8876858. The past as prelude to the future: history, status, and future of ***antiviral*** drugs. Whitley R J. (University of Alabama at Birmingham 35233, USA.) ANNALS OF PHARMACOTHERAPY, (1996 Sep) 30 (9) 967-71. Ref: 9. Journal code: BBX; 9203131. ISSN: 1060-0280. Pub. country: United States. Language: English.

AB OBJECTIVE: To ***review*** the first generation of ***antiviral*** agents (e.g., idoxuridine, amantadine, vidarabine) that paralleled discovery of antineoplastic agents. DATA SOURCES: A MEDLINE search (1962 to 1996) of the English-language literature pertaining to ***antiviral*** agents was performed. DATA EXTRACTION: All articles were considered for this ***review*** . Pertinent references on ***antiviral*** therapy, as judged by the author, were selected. DATA SYNTHESIS: Acyclovir, the first second-generation ***antiviral*** agent, has a known selective mechanism of action and provides the model for development of future ***antiviral*** therapies. Despite the safety and ***clinical*** value of acyclovir, therapy does not prevent establishment of latency or decrease frequency of occurrences, ***resistance*** has been documented, and outcome is frequently poor. With the emergence of the ***HIV*** /AIDS epidemic, several antiretroviral agents have been developed and approved. However, none of the four available nucleoside analogs provides a cure. CONCLUSIONS: Viral ***resistance*** has emerged as an important component of ***antiviral*** therapy. Improved therapies for cytomegalovirus are needed. Several new therapies for herpes zoster, including prodrugs, are licensed or in Phase III ***clinical*** trials. Future directions include the use of molecular biologic techniques to identify enzymes unique to viral replication and to accelerate diagnosis of viral diseases.

L34 ANSWER 44 OF 72 MEDLINE
97012618 Document Number: 97012618. PubMed ID: 9182098. ***Antiviral*** ***resistance*** : mechanisms, ***clinical*** significance, and future implications. Kimberlin D W; Whitley R J. (Department of Pediatrics, The University of Alabama at Birmingham, 35233, USA.) JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, (1996 Mar) 37 (3) 403-21. Ref: 144. Journal code: HD7; 7513617. ISSN: 0305-7453. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The increased awareness of ***antiviral*** ***resistance*** over the past decade has paralleled the development of new ***antiviral*** agents. While such ***resistant*** viral isolates are of ***clinical*** significance primarily in immunocompromised individuals, the development and transmission of such mutants have been reported in immunocompetent persons as well. As ***antiviral*** agents are increasingly utilised by the ***clinician*** , the incidence of such occurrences is likely to increase. Issues relating to mechanisms of ***antiviral*** ***resistance*** , ***clinical*** manifestations and significance of ***resistance*** , and implications for future ***antiviral*** development and utilisation are ***reviewed*** in this article. Viruses that are discussed include herpes simplex virus, varicella-zoster virus, cytomegalovirus, influenza A virus, and ***human*** ***immunodeficiency*** ***virus*** .

L34 ANSWER 46 OF 72 MEDLINE
96272955 Document Number: 96272955. PubMed ID: 8656507. Antiretroviral therapy for ***HIV*** infection in 1996. Recommendations of an international panel. International AIDS Society-USA. Carpenter C C; Fischl M A; Hammer S M; Hirsch M S; Jacobsen D M; Katzenstein D A; Montaner J S; Richman D D; Saag M S; Schooley R T; Thompson M A; Vella S; Yeni P G;

Volberding P A. (Brown University School of Medicine, Providence, RI, USA.) JAMA, (1996 Jul 10) 276 (2) 146-54. Ref: 109. Journal code: KFR; 7501160. ISSN: 0098-7484. Pub. country: United States. Language: English.

AB OBJECTIVE--To provide ***clinical*** recommendations for antiretroviral therapy for ***human*** ***immunodeficiency*** ***virus*** (***HIV***) disease with currently (mid 1996) available drugs. When to start therapy, what to start with, when to change, and what to change to were addressed. PARTICIPANTS--A 13-member panel representing international expertise in antiretroviral research and ***HIV*** patient care was selected by the international AIDS Society-USA. EVIDENCE--Available ***clinical*** and basic science data, including phase 3 controlled trials, ***clinical*** endpoint data, virologic and immunologic endpoint data, interim analyses, studies of ***HIV*** pathophysiology, and expert opinions of panel members were considered. Recommendations were limited to drugs available in mid 1996. PROCESS--For each question posed, 1 or more member(s) ***reviewed*** and presented available data. Recommendations were determined by group consensus (January 1996); revisions as warranted by new data were incorporated by group consensus (February-May 1996). CONCLUSIONS--Recent data on ***HIV*** pathogenesis, methods to determine plasma ***HIV*** RNA, ***clinical*** trial data, and availability of new drugs point to the need for new approaches to treatment. Therapy is recommended based on CD4+ cell count, plasma ***HIV*** RNA level, or ***clinical*** status. Preferred initial drug regimens include nucleoside combinations; at present protease inhibitors are probably best reserved for patients at higher progression risk. For treatment ***failure*** or drug intolerance, subsequent regimen considerations include reasons for changing therapy, available drug options, disease stage, underlying conditions, and concomitant medication(s). Therapy for primary (acute) infection, high-risk exposures to ***HIV*** , and maternal-to-fetal transmission are also addressed. ***Therapeutic*** approaches need to be updated as new data continue to emerge.

L34 ANSWER 47 OF 72 MEDLINE
95281268 Document Number: 95281268. PubMed ID: 7761142. ***Resistance*** to ***antivirals*** . Laufer D S; Starr S E. (Division of Allergy, Immunology, and Infectious Diseases, Children's Hospital of Philadelphia, Pennsylvania, USA.) PEDIATRIC CLINICS OF NORTH AMERICA, (1995 Jun) 42 (3) 583-99. Ref: 76. Journal code: OUM; 0401126. ISSN: 0031-3955. Pub. country: United States. Language: English.

AB The ability of viruses to develop ***resistance*** to ***antiviral*** agents is already a major concern with respect to ***HIV*** . This article ***reviews*** mechanisms and ***clinical*** correlates of ***antiviral*** ***resistance*** and alternative drugs for treatment of infections due to ***resistant*** strains of ***HIV*** , herpes simplex virus, cytomegalovirus, varicellazoster virus, and influenza A.

L34 ANSWER 51 OF 72 MEDLINE
95055006 Document Number: 95055006. PubMed ID: 7965648. Pathogenicity and diversity of ***HIV*** and implications for ***clinical*** management: a ***review*** . Saag M S; Hammer S M; Lange J M. (UAB AIDS Outpatient Clinic, University of Alabama at Birmingham 35294-2050.) JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES, (1994) 7 Suppl 2 S2-10; discussion S10-1. Ref: 36. Journal code: JOF; 8812597. ISSN: 0894-9255. Pub. country: United States. Language: English.

AB Genetic variation of ***human*** ***immunodeficiency*** ***virus*** (***HIV***) over time is an important consideration in

long-term antiretroviral therapy, in all likelihood affecting the course of ***HIV*** disease and its response to antiretroviral therapy. Viral replication persists throughout ***HIV*** disease, and viral burden is correlated with disease stage. CD4+ T-helper cells, a prime target for ***HIV*** , appear responsible for direct cellular and humoral responses to infection. ***HIV*** can be divided into three groups: nonsyncytium-inducing (NSI) isolates with low replicative capacity; high-replicative-capacity NSI isolates; and high-replicative-capacity, syncytium-inducing (SI) isolates. The SI phenotype also is associated with T-helper-cell tropism, rapid CD4+ cell count decline, and rapid ***HIV*** disease progression. In some ***HIV*** -infected individuals, SI variants evolve from NSI variants at approximate mean CD4+ cell counts of 400 to 500 cells/microliters. Appearance of SI variants may be a useful prognostic marker for decline in cell counts and more rapid progression to AIDS. However, SI variants are not required for ***HIV*** disease progression. Only about one-half of AIDS patients harbor SI variants, indicating that ***HIV*** that remains NSI can cause AIDS and death. Zidovudine ***resistance*** has been found (in ACTG 116B/117) to be an independent predictor of ***HIV*** disease progression. Zidovudine ***resistance*** and SI phenotype together are closely associated with rapid ***HIV*** disease progression.

L34 ANSWER 52 OF 72 MEDLINE
95035224 Document Number: 95035224. PubMed ID: 7948142. Gene therapy for ***human*** ***immunodeficiency*** ***virus*** infection: genetic ***antiviral*** strategies and targets for intervention. Dropulic B; Jeang K T. (Molecular Virology Section, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.) HUMAN GENE THERAPY, (1994 Aug) 5 (8) 927-39. Ref: 128. Journal code: A12; 9008950. ISSN: 1043-0342. Pub. country: United States. Language: English.

AB Gene ***therapeutic*** strategies for the treatment of ***human*** ***immunodeficiency*** ***virus*** type 1 (***HIV*** -1) infection have received increased attention due to lack of chemotherapeutic drugs or vaccines that show long-term efficacy in vivo. An emerging group, referred to here as "genetic ***antivirals*** ," is ***reviewed*** . Genetic ***antivirals*** are defined as DNA or RNA elements that are transferred into cells and affect their intracellular targets either directly, or after expression as RNA or proteins. They include antisense oligonucleotides, ribozymes, RNA decoys, transdominant mutants, toxins, and immunogens. They offer the possibility to target simultaneously multiple sites in the ***HIV*** genome, thereby minimizing the production of ***resistant*** viruses. We ***review*** the molecular mechanisms of genetic ***antivirals*** , their ***HIV*** molecular targets, and discuss issues concerning their application as anti- ***HIV*** agents.

L34 ANSWER 55 OF 72 MEDLINE
94226206 Document Number: 94226206. PubMed ID: 7513499. Pharmacologic therapy for ***human*** ***immunodeficiency*** ***virus*** infection: a ***review*** . Neuzil K M. (Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-2005.) AMERICAN JOURNAL OF THE MEDICAL SCIENCES, (1994 May) 307 (5) 368-73. Ref: 44. Journal code: 3L2; 0370506. ISSN: 0002-9629. Pub. country: United States. Language: English.

L34 ANSWER 57 OF 72 MEDLINE
93307093 Document Number: 93307093. PubMed ID: 7686460. ***Antiviral*** therapy in ***human*** ***immunodeficiency*** ***virus*** infections. Current status (Part II). Sandstrom E; Oberg B. (Department of

Dermatovenerology, Sodersjukhuset, Stockholm, Sweden.) DRUGS, (1993 May) 45 (5) 637-53. Ref: 235. Journal code: EC2; 7600076. ISSN: 0012-6667. Pub. country: New Zealand. Language: English.

AB Part I of this article ***reviewed*** the targets against which anti-***HIV*** drugs can be directed, problems in assessing active compounds (e.g. ***resistance*** development and use of surrogate end-points). and nucleoside analogues effective against ***HIV*** reverse transcriptase. Intensive research is currently being undertaken in laboratories and hospitals to design and evaluate new inhibitors of ***HIV*** . In this work, combining different drugs is one important approach, both to decrease toxicity and to offset the rate of ***resistance*** development, which seems to be a major problem associated with therapy directed against the ever-changing ***HIV*** . ***Therapeutic*** vaccines and immunomodulators are other modalities being actively evaluated against ***HIV*** and AIDS, although this effort has not yet yielded any licensed treatment. It appears likely that new ***antiviral*** drugs and immunotherapies will be forthcoming during the next 5 years, that they will be used in a variety of combinations, and that the treatment options available for opportunistic infections will increase. These developments should improve the survival and the quality of life of patients with ***HIV*** infection.

L34 ANSWER 60 OF 72 MEDLINE
93075898 Document Number: 93075898. PubMed ID: 1280169. Non-nucleoside inhibitors of ***HIV*** reverse transcriptase: screening successes--***clinical*** ***failures*** . Saunders J. (Department of Medicinal Chemistry II, Glaxo Group Research, Greenford, Middlesex, UK.) DRUG DESIGN AND DISCOVERY, (1992 Jul) 8 (4) 255-63. Ref: 19. Journal code: A5B; 9200627. ISSN: 1055-9612. Pub. country: Switzerland. Language: English.

AB A little less than two years ago, the first report describing non-nucleoside inhibitors of ***HIV*** reverse transcriptase (RT) led to the high anticipation that a range of new drugs could soon be available for the treatment of AIDS. **The intervening period has given rise to several such agents but recent ***clinical*** trial data has indicated this optimism to be premature**. This short ***review*** seeks to trace the brief history of the drug discovery process and to assess whether there are lessons to be learnt from the episode.

L34 ANSWER 64 OF 72 MEDLINE
92135627 Document Number: 92135627. PubMed ID: 2519841. Acquired immunodeficiency syndrome: molecular biology and its ***therapeutic*** intervention (***review***). Schulhafer E P; Verma R S. (Department of Allergy and Immunology, Long Island College Hospital, SUNY, Brooklyn 11201.) IN VIVO, (1989 Mar-Apr) 3 (2) 61-78. Ref: 100. Journal code: A6F; 8806809. ISSN: 0258-851X. Pub. country: Greece. Language: English.

AB AIDS is one of the most perplexing diseases to confront modern medicine today. AIDS will rank just behind accidents, heart disease and cancer as a major cause of potential life lost in the USA by 1991. Over half million AIDS cases are predicted by 1993 in the United States alone. There has been a great improvement in the understanding and treatment of opportunistic infections in AIDS. The most important concept is prophylactic treatment of the most common infectious complications as the immune system deteriorates. The major advance has been the prophylactic treatment of Pneumocystic Carinii Pneumonia (PCP) with either aerosolized Pentamidine or low dose Bactrim. Some experts advocate a low dose antibiotic prophylaxis for latent toxoplasma and cryptococcal infection in those patients whose immune systems are deteriorating. Prophylaxis would

be instituted as the T4 helper lymphocyte count decreases. Finally, any patient found to be lately infected with either tuberculosis or syphilis, while ***HIV*** positive, must be thoroughly treated for these infections prior to any immunocompromise. The minimum follow-up of ***HIV*** positive individuals should include T4 lymphocyte counts and perhaps P24 antigen levels as well as beta 2-microglobulin levels. As these parameters worsen, patients should be directed to explore safe available treatments such as Antabuse, Naltrexone and Dextran sulfate. Any healthy patient with T4 helper counts under 400 should be directed to AIDS treatment evaluation units for enrolment in research protocols. At present over 100 drugs are being tested for the treatment of AIDS. However, researchers predict that no more than one or two drugs will be discovered over the next three years that will be helpful in the treatment of AIDS. If ever there was a more powerful argument to institute a new way of evaluating research drugs, it is this prediction. Due to the epidemic proportions of this disease, it seems reasonable to test epidemic proportions of this disease, it seems reasonable to test drugs shown to have some effect in groups of three of four drugs per patient. It is well demonstrated that AZT (Zidovudine) loses its anti- ***retroviral*** effect at about twelve to eighteen months. Drug ***resistance*** is seen in the treatment of a similar infectious agent, M. tuberculosis. Acute infection of MTB necessitates the use of three antibacterial agents. In AIDS infection, it seems logical to test two or three anti- ***retrovirals*** combined with one immunostimulant.(ABSTRACT TRUNCATED AT 400 WORDS)

L34 ANSWER 66 OF 72 MEDLINE
91334060 Document Number: 91334060. PubMed ID: 1870944. ***Antiviral*** drugs. Wiltink E H; Janknegt R. (Department of Pharmacy, University of Medical Centre, Amsterdam, The Netherlands.) PHARMACEUTISCH WEEKBLAD. SCIENTIFIC EDITION, (1991 Apr 26) 13 (2) 58-69. Ref: 47. Journal code: OZW; 7907992. ISSN: 0167-6555. Pub. country: Netherlands. Language: English.

AB **There are only a limited number of effective, non-toxic ***antiviral*** drugs for ***clinical*** use, whereas there is a great need for such drugs. Especially for the treatment of patients infected with the human immuno-deficiency virus (***HIV***) anti- ***HIV*** drugs are required. At the same time viral infections secondary to AIDS cannot yet be treated effectively. An increasing problem is the development of virus strains ***resistant*** to the available drugs.** At this moment a great effort is made in the research for new ***antiviral*** drugs. In this article the available ***antiviral*** drugs are ***reviewed*** . Their ***antiviral*** properties, mechanism of action, ***clinical*** use, pharmacokinetic properties and side-effects are discussed. Some attention is paid to the future directions in the search for new anti- ***HIV*** drugs.

L34 ANSWER 70 OF 72 MEDLINE
90253455 Document Number: 90253455. PubMed ID: 2187439. Strategies in therapy and immunoprophylaxis of ***human*** ***immunodeficiency*** ***virus*** infection. Ferdinand F J. (Paul-Ehrlich-Institut, Bundesamt fur Sera und Impfstoffe, Langen, Fed. Rep. of Germany.) ARZNEIMITTEL-FORSCHUNG, (1990 Jan) 40 (1) 106-10. Ref: 40. Journal code: 91U; 0372660. ISSN: 0004-4172. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB In designing ***antiviral*** drugs and ***therapeutic*** schemes some basic considerations should be taken into account: 1. RNA viruses and especially ***HIV*** (***Human*** ***Immunodeficiency***

Virus) respond to environmental changes with evading mutations, hence, the high degree of variability of these viruses. All drugs interfering with viral functions will presumably give rise to ***resistant*** variants. 2. Approaches using cytotoxic peptides may induce adverse immune responses. Vaccines may elicit neutralizing antibodies, cellular cytotoxic responses, or both. The limitations of subunit vaccines or oligopeptides in eliciting cell mediated cytotoxicity in all vaccinees are outlined. Recent developments and the suitability of the ***SIV*** mac/rhesus monkey model are ***reviewed*** . The importance of adjuvants is indicated.

L34 ANSWER 71 OF 72 MEDLINE
89377897 Document Number: 89377897. PubMed ID: 2550235. Persistent herpes simplex virus infection and mechanisms of virus drug ***resistance*** . Field H J. (Department of Clinical Veterinary Medicine, Cambridge, UK.) EUROPEAN JOURNAL OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES, (1989 Aug) 8 (8) 671-80. Ref: 80. Journal code: EM5; 8804297. ISSN: 0934-9723. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB Herpes simplex virus (HSV) is susceptible to a variety of ***antiviral*** compounds, most of which are nucleoside analogues that interfere with DNA metabolism involving the virus enzymes DNA-polymerase and thymidine kinase. Single mutations in the virus genome give rise to ***resistant*** mutants following selection in vitro in the presence of a particular drug, and in this respect HSV is similar to several other viruses. Such mutants have been invaluable research tools. HSV is responsible for a variety of lesions which tend to be recurrent, owing to the special ability of the virus to remain latent in and reactivate from neural tissue. The consequences of this upon ***clinical*** ***resistance*** are discussed in the present ***review*** . In fact, ***clinical*** ***resistance*** in HSV infections has not yet become widespread but does appear to be especially important in immunocompromised patients, including those suffering from AIDS. HSV is proposed as an important model for the investigation of drug ***resistance*** in other, more complex organisms, and with respect to ***antiviral*** strategies against the ***human*** ***immunodeficiency*** ***virus*** .

L34 ANSWER 72 OF 72 MEDLINE
88054744 Document Number: 88054744. PubMed ID: 2824170. ***Antiviral*** therapy in AIDS. ***Clinical*** pharmacological properties and ***therapeutic*** experience to date. Sandstrom E G; Kaplan J C. (Department of Dermatology, Sodersjukhuset, Karolinska Institute, Stockholm.) DRUGS, (1987 Sep) 34 (3) 372-90. Ref: 85. Journal code: EC2; 7600076. ISSN: 0012-6667. Pub. country: New Zealand. Language: English.

AB The rapid spread of ***human*** ***immunodeficiency*** ***virus*** (***HIV***) infections and the grim outcome of these infections have focused interest on the possibilities for medical intervention. The end-stage of these infections, acquired immune deficiency syndrome (AIDS), was first recognised in 1981, and the causative agent isolated in 1983. Already several ***antiviral*** drugs have been investigated. One initially promising drug, suramin, was found to have a net harmful effect but another, zidovudine (azidothymidine) has been shown to prolong life in AIDS patients. The properties of these and several other ***antiviral*** drugs such as antimoniotungstate (HPA-23), foscarnet (phosphonoformate) ribavirin, dideoxynucleotides, and interferons, are ***reviewed*** . The role of immunomodulating modalities such as plasmapheresis, bone marrow transplantation, thymosin, interleukin-2, inosine pranobex (isoprinosine),

and cyclosporin are also discussed. None of the currently available drugs hold promise as monotherapy. Through analysis of the experience with these drugs and the increasing knowledge of ***HIV*** pathogenesis, new drugs can be designed. It seems increasingly clear that drugs will eventually have to be used in combination in order to reduce toxicity, exploit ***therapeutic*** synergy, and reduce the risk of ***HIV*** ***resistance*** . The theoretical and experimental background for such combinations are currently being elucidated.

L36 ANSWER 15 OF 109 MEDLINE
2000492525 Document Number: 20433582. PubMed ID: 10979204. Current status and future issues in the treatment of ***HIV*** -1 infection. Matsushita S. (Department of Clinical Retrovirology and Infectious Diseases, Kumamoto University, Japan.) INTERNATIONAL JOURNAL OF HEMATOLOGY, (2000 Jul) 72 (1) 20-7. Ref: 27. Journal code: A7F; 9111627. ISSN: 0925-5710. Pub. country: Ireland. Language: English.

AB Over the past 5 years, advances in ***human*** ***immunodeficiency*** ***virus*** type 1 (***HIV*** -1) ***clinical*** research and data on the effectiveness of potent combination therapy have substantially influenced the overall perspective of the long-term management of ***HIV*** -1 disease. It is now generally accepted that the benefits of mono- and bio-therapy for ***HIV*** -1 infection are only transient owing mainly to ***antiviral*** -drug ***resistance*** . To obtain continued benefit from ***antiviral*** therapy, current guidelines recommend at least triple-drug combinations, or so-called highly active antiretroviral therapy (HAART). In Japan, 13 antiretroviral agents are currently available for combination therapy. Ten of them have been approved for ***clinical*** use in the past 3 years. Following the introduction of HAART, marked decreases in AIDS-related morbidity and mortality have been observed. However, in some patients, HAART can be problematic, either because it is difficult for the patient to remain compliant or because previous suboptimum therapies have limited the choice of drugs. For compliant, drug-naive patients, HAART should offer long-term virus suppression, when changing from first- to second- to third-line HAART following drug ***failure*** . Long-term treatment might ultimately result in multidrug ***resistance*** , leaving few options for salvage therapy. ***HIV*** -1 drug ***resistance*** testing to enable salvage therapy and the development of new drugs and immunotherapeutic agents to allow new options will therefore remain priorities in ***HIV*** -1 research.

L36 ANSWER 17 OF 109 MEDLINE
2000417665 Document Number: 20318453. PubMed ID: 10860900. Pharmacodynamics of ***human*** ***immunodeficiency*** ***virus*** type 1 protease inhibitors. Acosta E P; Kakuda T N; Brundage R C; Anderson P L; Fletcher C V. (College of Pharmacy, Department of Experimental and Clinical Pharmacology, University of Minnesota Academic Health Sciences Center, Minneapolis, MN 55455, USA.. fletc001@tc.umn.edu) . CLINICAL INFECTIOUS DISEASES, (2000 Jun) 30 Suppl 2 S151-9. Ref: 37. Journal code: A4J; 9203213. ISSN: 1058-4838. Pub. country: United States. Language: English.

AB Many factors are involved in the success or ***failure*** of antiretroviral therapy. Recent data suggest that there are significant differences in drug absorption and disposition for the protease inhibitor class of antiretroviral drugs, and relationships between plasma concentrations and their ***antiviral*** effect have been described. Consequently, the issue of whether ***therapeutic*** drug monitoring should be employed for patients receiving treatment with these drugs has

arisen. Several criteria must be met before a drug is considered a candidate for ***therapeutic*** drug monitoring. These criteria include pharmacological, ***clinical*** , and analytic components. Although not all the necessary criteria have yet been met, some of these components have been defined, and additional data are being generated. However, prospectively designed ***clinical*** trials must be completed to determine if monitoring protease inhibitor plasma concentrations provides additional ***clinical*** benefit to the patient.

L36 ANSWER 18 OF 109 MEDLINE
2000340286 Document Number: 20340286. PubMed ID: 10885760. Immune reconstitution in ***HIV*** infection. Gea-Banacloche J C; Clifford Lane H. (Clinical and Molecular Retrovirology Section, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA.) AIDS, (1999) 13 Suppl A S25-38. Ref: 163. Journal code: AID; 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The weight of the published evidence suggest that there is ***clinically*** significant immune recovery in a sizable fraction of ***HIV*** -infected patients who achieve suppression of viral replication. At the same time, it is clear that very few patients regain normal (i.e. equivalent to pre-infection) immune function, at least after the follow-up periods available so far. The experience from bone-marrow transplantation or intensive chemotherapy in adults suggests that such kind of immune reconstitution is unlikely (at least with treatments limited to stopping virus replication) once the immune system has been sufficiently damaged. It is also clear that effective immunity to ***HIV*** is not achieved in a significant proportion of patients. These findings have implications for both basic research and ***clinical*** practice. From the laboratory perspective, besides the urgent need to characterize the protective immunity to ***HIV*** (if it exists), it would be desirable to find some simple measure of the immune function of patients who receive therapy. The combination of markers of immune activation together with CD4 cell count and viral load should be further evaluated in this context. Regarding ***clinical*** practice, it is likely that prophylaxes for opportunistic infections can be discontinued ***uneventfully*** in the majority of patients responding to HAART. Although the evidence is not yet conclusive, all available data suggest this will be the case. Given that there is significant immune reconstitution even in advanced disease, it is tempting to consider if this fact can be used to support ***antiviral*** therapy recommendations that are less aggressive than the current ones. ***HIV*** eradication by pharmacologic means alone does not seem possible yet, and no effective immune response to ***HIV*** seems to be generated by starting therapy in the asymptomatic (as opposed to acute infection) stage of the disease. At the same time, the follow-up studies on prolonged antiretroviral therapy suggest that virologic ***failure*** will take place despite many months of seemingly adequate suppression. This fact, taken together with the side effects and inconvience of current antiretroviral regimens, can be used to support an argument in favor of evaluating strategies to treat later rather than earlier.

L36 ANSWER 56 OF 109 MEDLINE
1998191622 Document Number: 98191622. PubMed ID: 9530544. Antiretroviral therapy for ***HIV*** infection. A knowledge-based approach to drug selection and use. Moyle G J; Gazzard B G; Cooper D A; Gatell J. (Kobler Centre, Chelsea and Westminster Hospital, London, England.) DRUGS, (1998 Mar) 55 (3) 383-404. Ref: 170. Journal code: EC2; 7600076. ISSN: 0012-6667. Pub. country: New Zealand. Language: English.

AB In the absence of evidence that eradication of ***HIV*** from an infected individual is feasible, the established goal of antiretroviral therapy is to reduce viral load to as low as possible for as long as possible. Achieving this with the currently available antiretroviral agents involves appropriate selection of components of combination regimens to obtain an optimal ***antiviral*** response. In addition, consideration of a plan for a salvage or second-line regimen is required if initial therapy ***fails*** to achieve an optimal response or should loss of virological control occur despite effective initial therapy. Such a planned approach, based on consideration of the likely modes of ***therapeutic*** ***failure*** (viral ***resistance*** , cellular ***resistance*** , toxicity) could be called rational sequencing. Choice of therapy should never involve compromise in terms of activity. However, the choice of drug should also be guided by tolerability profiles and considerations of coverage of the widest range of infected cells, compartmental penetration, pharmacokinetic interactions and, importantly, the ability of an agent or combination to limit future ***therapeutic*** options through selection of cross- ***resistant*** virus. Available ***clinical*** end-point data clearly indicate that combination therapy is superior to monotherapy, with ***clinical*** and surrogate marker data supporting the use of triple drug (or double protease inhibitor) combinations over double nucleoside analogue combinations. Thus, 3-drug therapy should represent current standard practice in a nontrials setting. Treatment should be considered as early as practical, and may be best guided by measurement of viral load, with a range of other markers having potential utility in individualising treatment decisions. ***Therapeutic*** ***failure*** may be defined ***clinically*** , immunologically or, ideally, virologically, and should prompt substitution of at least 2, and preferably all, components of the treatment regimen. Drug intolerance may also be best managed by rational substitution.

L36 ANSWER 71 OF 109 MEDLINE
96261397 Document Number: 96261397. PubMed ID: 8815703. Antiretroviral drug ***resistance*** : mechanisms, pathogenesis, ***clinical*** significance. Richman D D. (San Diego Veterans Affairs Medical Center, La Jolla, California, USA.) ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1996) 394 383-95. Ref: 94. Journal code: 2LU; 0121103. ISSN: 0065-2598. Pub. country: United States. Language: English.

AB The contribution of ***HIV*** drug ***resistance*** to treatment ***failure*** , the relationship of drug ***resistance*** to pathogenesis and the impact of ***resistance*** in the role of the promising new class of protease inhibitors remain areas of active investigation. A more precise understanding of these aspects of antiretroviral drug ***resistance*** will permit the more effective use of available drugs and the design of new drugs and drug regimens.

L36 ANSWER 80 OF 109 MEDLINE
96099876 Document Number: 96099876. PubMed ID: 7495676. Discovery and in vitro development of AIDS ***antiviral* drugs as biopharmaceuticals. Rice W G; Bader J P. (Laboratory of Antiviral Drug Mechanisms, National Cancer Institute, Frederick Cancer Research and Development Center, Maryland 21701-1201, USA.) ADVANCES IN PHARMACOLOGY, (1995) 33 389-438. Ref: 204. Journal code: AXI; 9015397. ISSN: 1054-3589. Pub. country: United States. Language: English.**

AB The goal of developing an effective drug against ***HIV*** -1 and AIDS has been approached by several routes, with enough encouraging results to stimulate further efforts. Compounds active against ***HIV*** -1 have

been discovered for many of the functions in the reproductive cycle recognized as virus-specific targets. Discoveries have been made in cell-based assays as well as mechanistic assays, and the value of both types of assays in the drug discovery process has been discussed. Although **the final test of a drug's efficacy comes in the ***clinical*** experience**, submission of an ***antiviral*** compound to an in vitro developmental gauntlet can save much time, effort, expense, and human resource in the in vivo developmental regimen required prior to human use. Emergence of viral ***resistance*** to drugs in several structural classes has compromised their ***clinical*** efficacy, suggesting that development of other potential drugs in those classes may not be good investments. Strains of ***HIV*** -1 ***resistant*** to specific compound classes are used to categorize new active discoveries for possible developmental exclusion, and defining the mechanism of action of such a new compound may confirm the discouraging judgement. On the other hand, novel compounds which exhibit a broad range of activity in drug- ***resistant*** and other ***HIV*** -1 strains deserve greater scrutiny. *****Clinicians*** most likely will be hesitant to treat patients with compounds shown to act on virus-cell surface interactions, given the ***failure*** in the past of several such compounds in ***clinical*** studies**. But a compound shown to have a unique and novel mechanism of action will be looked upon more favorably, and surviving other tests of potency, solubility, and stability will be unhesitatingly presented for in vivo development. The partial successes of drugs currently in ***clinical*** use against AIDS offers great encouragement that other more-effective, less-toxic drugs will be found. Exquisite techniques for identifying new targets on virus gene products, the selection of compounds on activity paradigms, and the enormous variety of compounds becoming available through synthesis libraries, all offer opportunities for anti- ***HIV*** drug discovery, which, in our view, cannot ***fail*** to present potent ***antiviral*** compounds which will survive the rigorous preclinical and ***clinical*** tests leading to a drug effective against AIDS.

L36 ANSWER 81 OF 109 MEDLINE
96089203 Document Number: 96089203. PubMed ID: 7488557. ***HIV* viral load quantification, ***HIV*** ***resistance*** , and antiretroviral therapy. Katzenstein D A; Holodniy M. (Stanford University School of Medicine, California, USA.) AIDS CLINICAL REVIEW, (1995-96) 277-303. Ref: 107. Journal code: AYD; 8914235. ISSN: 1045-2877. Pub. country: United States. Language: English.**

AB We are moving rapidly beyond a "black box" understanding of the pathogenesis of ***HIV*** . The sites of virus replication, the molecular regulation of virus production in the host, and the dynamics between productive virus infection and immunological and ***clinical*** events are areas of intense study using powerful new tools. The quantitation of virus load and genetic characterization of replicating virus has important implications for the development and evaluation of drugs and treatment strategies for ***HIV*** . As new compounds are introduced, **their ability to reduce virus load in vivo has become a primary consideration in the decision to initiate large efficacy trials and may soon be used, in combination with other markers, in the licensing of new agents**. In parallel, rapid molecular evaluation of virus from patients, targeting those who break through drug-induced suppression, provides an explanation for the ***failure*** of drugs to sustain an effect on virus load. This approach has compressed the process of drug evaluation and set the stage for the evaluation of complex combinations and sequences of drugs to maintain suppression of virus and prevent the development of drug ***resistance*** . The most controversial question

for the next few years is whether the measurement of virus load or detection of drug ***resistance*** can be incorporated into the practice of medicine and the management of individual patients. There is evidence that changes in virus load are the most proximate markers of drug response and that detection of ***resistance*** mutations can predict ***clinical*** and immunological decline. However, the window of time between a change in load or the development of drug ***resistance*** and a decline in CD4 cells is relatively short. With dideoxynucleoside therapies, a CD4 cell decline follows a rise in virus load or development of ***resistance*** within 3-6 months. In early studies with protease inhibitors and nonnucleoside reverse transcriptase inhibitors, the development of ***resistance*** and a return to baseline of virus load may occur within 2-3 months, mirrored by a fall in CD4 cells. The challenge to investigators is how to best use these new tools to determine whether changes or additions in therapy, initiated on the basis of virological measurements, result in more effective management of disease.

L36 ANSWER 82 OF 109 MEDLINE
96022717 Document Number: 96022717. PubMed ID: 8586528. ***Failure*** of antiretroviral therapy: role of viral and cellular factors. Cinatl J Jr; Cinatl J; Rabenau H; Doerr H W; Weber B. (Institut fur Medizinische Virologie, Universitatskliniken Frankfurt, Deutschland.) INTERVIROLOGY, (1994) 37 (6) 307-14. Ref: 76. Journal code: GW7; 0364265. ISSN: 0300-5526. Pub. country: Switzerland. Language: English.

AB Effective therapy of ***human*** ***immunodeficiency*** ***virus*** (***HIV***) infection is mainly based on inhibition of reverse transcriptase by nucleoside analogues such as zidovudine (azidothymidine; AZT), didanosine, and zalcitabine. A major problem associated with long-term AZT therapy is the waning efficacy (' ***clinical*** ***resistance*** ') over time. ***Clinical*** isolates of ***HIV*** -1 with reduced susceptibility to AZT can be recovered from ***HIV*** -infected individuals under prolonged treatment. However, the ***clinical*** importance of AZT ***resistance*** is uncertain. Other factors such as increased virus burden, increased virulence, and AZT toxicity could contribute, singly or in combination, to the loss of ***therapeutic*** benefit. Recent observations based on experimental models and ***clinical*** trials suggest that cellular mechanisms ('cellular ***resistance*** ') may account for ***clinical*** ***resistance*** to ***antiviral*** agents. In vitro experiments demonstrated that in analogy to antitumoral therapy, the acquisition of multidrug ***resistance*** , i.e., ***resistance*** of cells to multiple, structurally unrelated chemotherapeutic agents, may play a role in the ***failure*** of long-term antiretroviral therapy. The 'cellular ***resistance*** ' may contribute directly to the ***failure*** of ***antiviral*** therapy by the generation of subtherapeutic levels of ***antiviral*** compounds and/or their active forms. Indirectly, such subtherapeutic concentrations of active substances which permit limited replication of virus may represent a selective pressure for emergence and development of a ***resistant*** virus population. Hence it is of great importance to investigate the role of cellular factors in ' ***clinical*** ***resistance*** ' to AZT and other anti- ***HIV*** agents. More detailed knowledge of cellular interactions and ***antiviral*** agents could help to improve or develop new strategies for ***antiviral*** therapy regimens.

L36 ANSWER 84 OF 109 MEDLINE
95353766 Document Number: 95353766. PubMed ID: 7627623. Mechanism of ***HIV*** persistence: implications for vaccines and therapy. Bremermann H J. (Department of Molecular and Cell Biology, University of California,

Berkeley, USA.) JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES AND HUMAN RETROVIROLOGY, (1995 Aug 15) 9 (5) 459-83. Ref: 67. Journal code: B7J; 9501482. ISSN: 1077-9450. Pub. country: United States. Language: English.

AB Periodic infusion of autologous ***HIV*** -antigen presenting cells (APCs), that stimulate the cytotoxic (CTL) response, while being incapable of producing virus, should lower viral burden and boost CD4+ count in ***HIV*** -seropositive individuals. Viral burden reasserts itself after ***antiviral*** therapy ceases or is interrupted for long. Therapy, therefore, would have to continue for life. These are predictions from a computer model of ***HIV*** -immune kinetics. The model equations describe the interactive kinetics of viral burden, CD4+ cell decline, neutralization of free virus by antibodies, infection of cells, and killing of infected cells by CTL. The computed trajectories of the kinetic equations reproduce the typical course of an ***HIV*** infection and the model yields several predictions that are not intuitively obvious, among them: (a) Persistence of ***HIV*** infection (***failure*** of the immune system to clear infection) is an intrinsic property of the kinetics of the ***HIV*** -immune interaction. (b) The chronic state of infection is inherently stable, which means that the infection rebounds to the determined steady state, whenever ***antiviral*** therapy stops. (c) CTL is chronically activated, and the level correlates inversely with the avidity of neutralizing antibodies. (d) APCs have to be infused at a rate such as to boost and maintain the CTL response above the chronic level. Other therapies include CTL stimulation, via the macrophage route, by erythrocytes, into which MHC binding ***HIV*** -CTL epitope polypeptide fragments have been inserted; passive immunization, virion-trapping by CD4 analogs or CD4 expressing erythrocytes; and combination therapies with AZT, IL-2. These are also analyzed. Concerning ***HIV*** etiology, the model assumes that cells other than CD4+ cells (such as macrophages/monocytes) become infected, and contribute to the viral burden, and that infectible cells remain available even as CD4+ cells become exhausted. The model further assumes that CD4+ cells decline not only through direct killing by ***HIV*** and CTL, but by dysregulation and excess apoptosis caused by the presence of virus. The model predicts that persistence of ***HIV*** infection does not depend upon latently infected cells or escape mutants, as has been suggested.(ABSTRACT TRUNCATED AT 400 WORDS)

L36 ANSWER 88 OF 109 MEDLINE
95110633 Document Number: 95110633. PubMed ID: 7811540.
Resistance , drug ***failure*** , and disease progression.
Richman D D. (Department of Pathology, University of California at San Diego, La Jolla 92093-0679.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1994 Aug) 10 (8) 901-5. Ref: 24. Journal code: ART; 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB The ***clinical*** significance of the reduced in vitro susceptibility of ***HIV*** to antiretroviral agents has been difficult to elucidate for nucleoside analogs such as zidovudine. However, the virological significance of ***resistance*** to nevirapine and other ***HIV*** -1-specific reverse transcriptase inhibitors has been established. With antiretroviral therapy, disease progression is not equivalent to drug ***failure*** , which is not equivalent to drug ***resistance*** . ***Clinical*** disease progression is only indirectly linked to ***HIV*** replication. Drug ***resistance*** is complex, and combining drugs does not appear to delay emergence of ***resistant*** strains of ***HIV*** although it may affect the specific amino acid substitutions. Drug ***resistance*** does appear to contribute to drug ***failure*** . The ***clinical*** trial ACTG 116B/117 found that the duration of prior zidovudine therapy was not related to the relative

benefit of switching to didanosine. Preliminary results of analysis of ***resistant*** strains of ***HIV*** isolated from ACTG 116B/117 patients revealed that the relative hazard of progression was about threefold higher for patients with high-level ***resistance*** to zidovudine, syncytium-inducing biological phenotype, and an AIDS diagnosis at baseline. This study showed clearly that acquisition of an ***HIV*** strain with high-level ***resistance*** to zidovudine was a poor prognostic factor. Although nevirapine ***resistance*** emerges rapidly, preliminary data suggest that high dosages may be active against ***HIV*** even in the presence of ***resistant*** ***HIV*** strains. At the present time, viral ***resistance*** and biological phenotype are not useful in the management of individual patients.

L36 ANSWER 89 OF 109 MEDLINE
95016001 Document Number: 95016001. PubMed ID: 7930696. ***Failure*** of short-term CD4-PE40 infusions to reduce virus load in ***human*** ***immunodeficiency*** ***virus*** -infected persons. Ramachandran R V; Katzenstein D A; Wood R; Batts D H; Merigan T C. (Center for AIDS Research, Stanford University Medical Center, California 94305.) JOURNAL OF INFECTIOUS DISEASES, (1994 Oct) 170 (4) 1009-13. Journal code: IH3; 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB The safety, immunologic, and ***antiviral*** effects of a recombinant biologic product that combines the second and third domains of the CD4 molecule and Pseudomonas exotoxin A (PE40) were evaluated in 21 ***human*** ***immunodeficiency*** ***virus*** (***HIV***)-infected subjects in a phase III open-label dose-ranging study. Subjects with CD4+ lymphocyte counts of 100-500/mm3 received CD4-PE40 at 40, 80, or 160 micrograms/m2 by infusion three to seven times over 10 days. At the maximum tolerated dose (80 micrograms/m2), peak CD4-PE40 levels were 65-130 ng/mL with a serum half-life of 3.6 +/- 1.5 h. Toxicity, primarily increased hepatic transaminases, was dose-related and reversible. ***HIV*** DNA proviral levels in peripheral blood mononuclear cells and plasma ***HIV*** RNA remained stable during and after CD4-PE40 infusions. **The relative ***resistance*** of ***clinical*** isolates of ***HIV*** , limits of the tolerated dose, and the immunogenicity and short half-life of the protein may explain the lack of in vivo ***antiviral*** effect of CD4-PE40.**

L36 ANSWER 90 OF 109 MEDLINE
95008667 Document Number: 95008667. PubMed ID: 7924193. ***HIV*** -1 burden as a marker of disease progression and ***clinical*** response to therapy in AIDS. Coombs R W. (Department of Laboratory Medicine, University of Washington, Seattle.) CLINICS IN LABORATORY MEDICINE, (1994 Jun) 14 (2) 301-11. Ref: 47. Journal code: DLS; 8100174. ISSN: 0272-2712. Pub. country: United States. Language: English.

AB In summary, much still needs to be learned about the pathogenetic significance of changes in virus load and importantly, the ***clinical*** significance of therapy-induced changes in virus load. **The ***failure*** of current ***therapeutic*** regimens to effect a substantive and durable change in virus load is not a ***failure*** of the virologic markers per se but is a call for better antiretroviral and immunotherapeutic-based approaches to treat infected patients.** At the same time, the experimental ***therapeutic*** regimens should be used to elucidate the unresolved pathogenetic nuances of ***HIV*** -1 burden that are a necessary prerequisite for developing a more effective containment of replicating ***HIV*** -1 and prolonging the lives of our ***HIV*** -1-infected patients.

L36 ANSWER 95 OF 109 MEDLINE
94207480 Document Number: 94207480. PubMed ID: 1344652.
Therapeutic aspects of ***retroviral*** disease. Peto T. (John Radcliffe Hospital, Headington, Oxford, UK.) BAILLIERES CLINICAL NEUROLOGY, (1992 Apr) 1 (1) 239-57. Ref: 88. Journal code: B0Z; 9214291. ISSN: 0961-0421. Pub. country: ENGLAND: United Kingdom. Language: English.

AB ***Retroviruses*** of the nervous system cause HTLV-1-associated myelopathy and ***HIV*** -associated diseases. The treatment of HTLV-1 disease is essentially conservative; there is no effective drug treatment and therefore patients should be simply supported and reassured. If appropriate, other members of the family should be tested for HTLV-1 disease and counselled. The effects of ***HIV*** on the nervous system are much more complex. Therapy must take account of the diverse complications of ***HIV*** disease. Patients are probably best managed in specialized ***clinics*** which can cope with the different manifestations of the disease. Zidovudine (AZT) is the only effective anti- ***HIV*** drug that is licensed. It is indicated in complicated seroconversion disease and for any manifestation of ***HIV*** progression including AIDS dementia complex. Management of severe neurological disease depends critically on the ability to diagnose and treat CNS-specific opportunistic infections. Whether zidovudine is indicated for early asymptomatic disease when CD4 counts are below 500 microliters-1 is controversial. The main problems of zidovudine are reversible anaemia which results in about 30% of patients not tolerating long-term use, and the **development of drug ***resistance*** ** which may be associated with ***clinical*** ***failure*** of the drug. **Other, new and experimental drug treatments are discussed but none of them has as yet shown any convincing evidence of efficacy**. Future improvements in treatment appear to depend on the development of effective multiple drug regimens (concurrently or sequentially) which will overcome the challenge of drug ***resistance*** .

L36 ANSWER 101 OF 109 MEDLINE
93262486 Document Number: 93262486. PubMed ID: 7684163. Present status and future prospects for ***HIV*** therapies. Johnston M I; Hoth D F. (Basic Research and Development Program, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, MD 20892.) SCIENCE, (1993 May 28) 260 (5112) 1286-93. Ref: 123. Journal code: UJ7; 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB Since the discovery of ***human*** ***immunodeficiency*** ***virus*** (***HIV***) in 1983, significant progress has been made toward the discovery, development, and licensing of anti- ***HIV*** drugs. In vitro screens against whole virus are now being complemented by screens against specific viral targets, resulting in the development of ***clinical*** candidates acting at several critical stages of the viral life cycle. Despite these advances, *****clinical*** therapy remains largely palliative**. In addition, it has recently been recognized that *****HIV*** ***resistance*** to most drugs may pose even greater obstacles**. Moreover, emerging data on immunopathogenesis raise the possibility that even if virus was eliminated from an infected individual, **the patient's immune system might not be capable of restoration to normal function**. In the face of such obstacles, deeper insights into the pathogenic mechanisms of disease, aggressive exploitation of those mechanisms for ***therapeutic*** gain, and continued commitment of both public and private sectors to support and collaborate in this research are needed.

L38 ANSWER 12 OF 71 MEDLINE
97189750 Document Number: 97189750. PubMed ID: 9037865. Preliminary ***screening*** for ***antiviral*** AIDS drugs. VI. Report for fiscal year 1993. Ushijima H; Takahashi K; Kunisada T; Moritugu Y; Kobayashi N; Noguchi Y; Matsuyama M; Akiyoshi K; Noro S; Sawada H; Sakurada N; Yamada A; Ishizaki T; Kamimura N; Yoshida Y; Ono T; Ohtomo N; Morishita T; Kobayashi S; Miyake T; Ishiwara Y; Suzuki R; Saito T; Etoh S; Mise K; +. EISEI SHIKENJO HOKOKU. BULLETIN OF NATIONAL INSTITUTE OF HYGIENIC SCIENCES, (1996) (114) 48-9. Journal code: BQ8; 0421152. ISSN: 0077-4715. Pub. country: Japan. Language: Japanese.

AB Preliminary ***screening*** of ***antiviral*** AIDS drugs has been carried out using three different in ***vitro*** assay systems. **Among 138 samples tested, two were found to inhibit the growth of ***HIV*** in ***vitro*** . Neither of the positive samples has hopeful signs, as the ranges of effective doses of the samples are very narrow.**

L38 ANSWER 38 OF 71 MEDLINE
95003486 Document Number: 95003486. PubMed ID: 7919786. Protein structure--based drug design. Whittle P J; Blundell T L. (Pfizer Central Research, Sandwich, Kent, United Kingdom.) ANNUAL REVIEW OF BIOPHYSICS AND BIOMOLECULAR STRUCTURE, (1994) 23 349-75. Ref: 72. Journal code: BH5; 9211097. ISSN: 1056-8700. Pub. country: United States. Language: English.

AB Design cycles will undoubtedly play an increasingly important role in drug discovery in the coming years, as the amount of structural information on protein targets continues to rise. However, the traditional method of drug discovery, based upon random ***screening*** and systematic modification of leads by medicinal chemistry techniques, will probably not be abandoned completely because it has a potentially important advantage over more structure-based methods--namely, leads identified in this way are unlikely to show a close resemblance to the natural ligand or substrate. They may, therefore, have advantages in terms of patent novelty, selectivity, or pharmacokinetic profile. However, such leads could then serve as the basis for structure-based, rational modification programs, in which their interactions with target receptors are defined (as we have described) and improved molecules are designed. A final important point to be made about structure-based design in drug discovery is that, **while it can be of great use in the initial process of identifying ligands with improved affinity and selectivity in ***vitro*** , it can usually say very little about other essential aspects of the drug discovery process, e.g. the need to achieve an adequate pharmacokinetic profile and low toxicity in ***vivo*** .** This observation reminds us that drug design is a multidisciplinary process, involving molecular biologists, biochemists, pharmacologists, organic chemists, crystallographers, and others. In order to be effective, therefore, structure-based design must be properly integrated into the overall discovery effort.

L39 ANSWER 7 OF 10 MEDLINE
93066274 Document Number: 93066274. PubMed ID: 1438243. A synthetic ***peptide*** ***inhibitor*** of ***human*** ***immunodeficiency*** ***virus*** replication: correlation between solution structure and viral inhibition. Wild C; Oas T; McDanal C; Bolognesi D; Matthews T. (Department of Surgery, Duke University Medical Center, Durham, NC 27710.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1992 Nov 1) 89 (21) 10537-41. Journal code: PV3; 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB A peptide designated DP-107 was synthesized containing amino acid residues 558-595 of the envelope glycoprotein gp160 of ***human*** ***immunodeficiency*** ***virus*** type 1 strain LAI (***HIV*** -1LAI). Algorithms for secondary structure have predicted that this region of the envelope transmembrane protein should form an extended alpha-helix. Consistent with this prediction, analysis by circular dichroism (CD) indicated that, under physiological conditions, DP-107 is approximately 85% helical. The high degree of stable secondary structure in a synthetic peptide of this size suggests self-association typical of a coiled coil or leucine zipper. In biological assays, the peptide efficiently blocked virus-mediated cell-cell fusion processes as well as infection of peripheral blood mononuclear cells by both prototypic and primary isolates of ***HIV*** -1. A single amino acid substitution in the peptide greatly destabilized its solution structure as measured by CD and abrogated its ***antiviral*** activity. An analogue containing a terminal cysteine was oxidized to form a dimer, and this modification lowered the dose required for ***antiviral*** effect from 5 to about 1 microgram/ml. These results suggest that both oligomerization and ordered structure are necessary for biological activity. They provide insights also into the role of this region in ***HIV*** infection and the potential for development of a new class of ***antiviral*** agents.